

# NEW THERAPIES IN ASTHMA



BY SUZANNE G. BOLLMEIER, PHARM.D., BCPS, AE-C

Reviewed by Wendy Brown, Pharm.D., MPAS, PA-C, AE-C; Autumn L. Stewart, Pharm.D., BCACP; and Nancy S. Yunker, Pharm.D., BCPS

## LEARNING OBJECTIVES

1. Evaluate interventions based on the etiologies, status, and control of asthma.
2. Develop and justify optimal therapeutic regimens based on the underlying pathophysiology of asthma and current evidence.
3. Devise an asthma education care plan for a patient or family member(s).
4. Demonstrate an understanding of pharmacogenomic testing and how results influence treatment decisions in patients with asthma
5. Demonstrate an understanding of emerging therapies in the treatment of asthma and judge when they would be applicable in patient care
6. Display insight into technological advances in asthma care and recommend them to patients when appropriate.

## INTRODUCTION

Asthma is an episodic yet chronic disease that places a heavy economic burden on patients, their families, and the

health care system. Asthma can influence quality of life by causing missed school or work days, medical expenses, and premature death. A growing body of knowledge about the pathophysiology, the hygiene hypothesis, and the environmental factors leading to the development of asthma has enabled researchers to better target future therapies.

Ambulatory care pharmacists have a unique opportunity to serve patients with asthma. The National Asthma Education and Prevention Program Expert Panel Report 3 (EPR-3) guidelines call for asthma self-management education to be integrated into all aspects of care (EPR-3 2007). With extensive education on asthma pathophysiology, therapeutics, and inhalation/device technique, the pharmacist is an integral part of the health care team providing education and helping maintain asthma control.

The impact of pharmacist-provided services for individuals with respiratory disorders has been documented. Pharmacist interventions lead to decreased symptoms and improvement in asthma severity (Benavides 2009). Pharmacist-driven medication therapy management

## BASELINE KNOWLEDGE STATEMENTS

Readers of this chapter are presumed to be familiar with the following:

- On the basis of a patient's specific medical history, interview, and objective findings, ascertaining asthma severity and current level of control, as well as preferred and alternative treatments, as established by National Asthma Education and Prevention Program EPR-3.
- Delineating the differences in inhaled steroid potency as low, medium, and high as established by EPR-3.
- Establishing approaches to address patient adherence (e.g., medication possession ratio), inhaler techniques (e.g., In-Check Dial, 2Tone Trainer), basic environmental control, and comorbid conditions before stepping up treatment.
- Identifying optimal step-down treatment in well-controlled patients.

## ADDITIONAL READINGS

The following free resources are available for readers wishing additional background information on this topic.

- National Asthma Education and Prevention Program [Expert Panel Report 3](#).
- [Global Initiative for Asthma Treatment Guidelines](#).
- QualityMetric. [Asthma Control Test](#).
- Merck. [Asthma Therapy Assessment Questionnaire](#).

## ABBREVIATIONS IN THIS CHAPTER

ACO	Accountable care organization
ADRB2	$\beta_2$ -Adrenergic receptor
Arg16	ADRB2 polymorphism
EPR-3	Expert Panel Report 3
FEV1	Forced expiratory volume in 1 second
FVC	Forced vital capacity
HFA	hydrofluoroalkane
ICS	Inhaled corticosteroid
LABA	Long-acting $\beta$ -agonist
NO	Nitric oxide
PEF	Peak expiratory flow
SABA	Short-acting $\beta$ -agonist
SMART	Single maintenance and reliever therapy
Th	T-helper (cell)
TLR	Toll-like receptor

services are also beneficial financially. The Asheville Project demonstrated that with increased spending on asthma drugs, a net savings resulted because of less absenteeism and fewer emergency department (ED) visits and hospitalizations (Bunting 2006). Pharmacists are uniquely situated within the health care team to care for patients with asthma.

The Affordable Care Act is establishing new models for delivering services to Medicare beneficiaries. An accountable care organization (ACO) is a network of doctors, hospitals, and other health care suppliers working together to coordinate and improve the quality of patient care. In this model, an ACO would be responsible for keeping patients healthy and out of the hospital. This involves a shift from the traditional fee-for-service structure to payments based on quality metrics and reductions in the total cost of care (Gold 2011). The ACO must meet quality standards in five areas: (1) patient/caregiver care experience, (2) care coordination, (3) patient safety, (4) preventive health, and (5) at-risk population/frail elderly health. Pharmacists working with providers in both outpatient and inpatient settings can aid ACOs by supporting initiatives that meet these standards. For example, improving adherence in the use of controller drugs and in applying appropriate device technique can decrease ED visits and hospitalizations for asthma. Clinical pharmacists in ACOs may also address drug-related issues by contracting to provide medication therapy management or medication reconciliation services.

## EPIDEMIOLOGY

It is estimated that in the United States, 18.7 million adults (8.2%) and 7 million children (9.4%) have asthma, and that 29.1 million adults (12.7%) and 10.1 million

children (13.6%) will receive a diagnosis of asthma during their lifetimes. The prevalence of asthma has risen by 14.8% in less than 10 years (2001 to 2010) (Asthma Impact on the Nation 2011).

## Incidence and Economic Impact

The incidence of asthma is disproportionately higher among children, women, individuals in lower-income socioeconomic groups, and the African American and Hispanic populations. The death rate, too, is highest among those patient groups. Asthma's economic impact is alarming: from 2002 to 2007, the annual cost was \$56 billion, with direct health care costs of \$50.1 billion and indirect costs of an additional, \$5.9 billion. The cost of asthma is not limited to medical and drug costs; lost productivity is also a major factor. According to the CDC, 59% of children and 33% of adults missed school or work because of asthma attacks in 2008. Annually, the average number of school days missed was 4, and work days missed averaged 5.

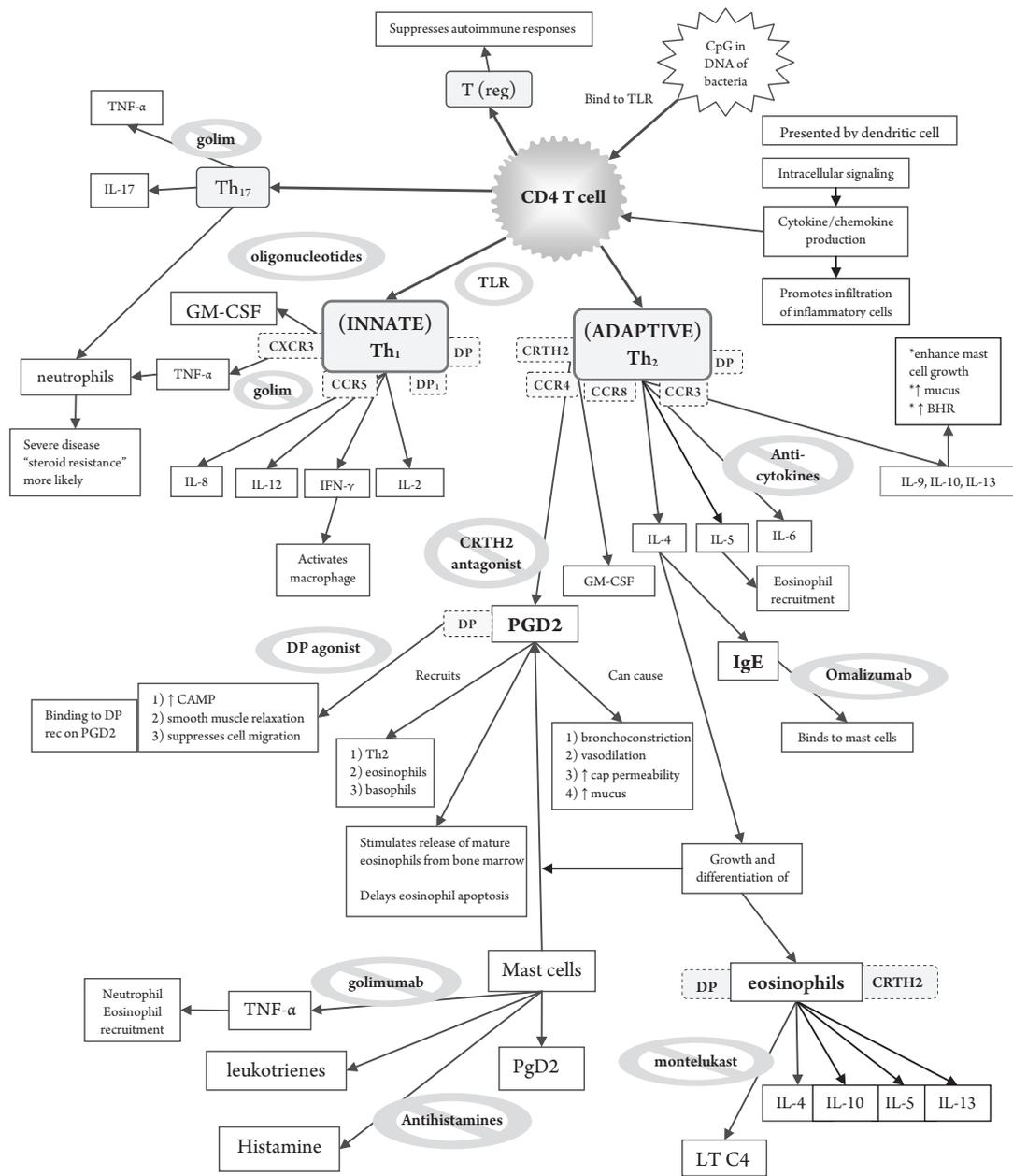
## PATHOPHYSIOLOGY

### Host Factors

Asthma is a complex compilation of signs and symptoms that are patient specific. The general etiologic factors that predispose a person to asthma are atopy and exposure to environmental triggers. Compared with developing nations, the incidence and prevalence of asthma are much higher in Western countries because of changes in lifestyles that include extremely clean household environments and fewer circulating infectious diseases. This so-called hygiene hypothesis is based on scientific observation that because of lack of exposure to infectious organisms, the immune system is no longer challenged adequately in children born in industrialized nations (Schroder 2008). In this model, the developing immune system shifts the balance between what would normally be equal parts of T-helper (Th) cells type 1 and type 2 (Okada 2010). The lack of exposure to bacteria shifts the immune system toward a Th2 cell-mediated immunity (Figure 1-1). This shift favors the development of allergic disorders, including asthma, because Th2 cells produce interleukins (i.e., IL-4, IL-5, IL-6, and IL-13) that contribute to atopy through immunoglobulin E production.

### Environmental Factors

Together with the hygiene hypothesis, the best evidence is that environmental influences can trigger asthma or predispose a person to asthma. These influences include exposure to allergens, inhalation of tobacco smoke, the presence of air pollution, and obesity. Indoor allergens associated with the development of asthma include mold, dust mites, animal dander (Gaffin 2009), and cockroaches (Gao 2011). House dust mites are highly allergenic antigens and cause the highest rates of positive skin-prick



**Figure 1-1.** The role of existing and emerging therapies in the inflammatory cascade.

**KEY**

Dashed line boxes = receptor;

⊖ = Antagonist / mechanism of action is blockade of the pathway

⊕ = Agonist / mechanism of action is promotion of the pathway

BHR = bronchial hyperresponsiveness, CAMP = cyclic adenosine monophosphate, CCR = chemokine receptor, CD4 = specific type of T immune cell, CpG = unmethylated sequences of DNA that have immunostimulatory properties, CRTH2 = chemoattractant receptor, CXCR3 = chemokine receptor CXCR3, DP = PgD2 receptor, DP1 = PgD2 receptor, GM-CSF = granulocyte-macrophage colony-stimulating factor, IFN- $\gamma$  = interferon gamma, IgE = immune globulin E, IL = interleukin, LT C4 = leukotriene C4, PgD2 = prostaglandin D2, T (reg) = regulatory T cell, Th = T helper cell, TLR = toll-like receptor, TNF $\alpha$  = tumor necrosis factor-alpha

Information from Arima M, Fukuda T. Prostaglandin D2 receptors DP and CRTH2 in the pathogenesis of asthma. *Curr Mol Med* 2008;8:365-75; Arima M, Fukuda T. Prostaglandin D2 and Th2 inflammation in the pathogenesis of bronchial asthma. *Korean J Int Med* 2011;26:8-18; Hansbro PM, Kaiko GE, Foster PS. Cytokine/anti-cytokine therapy—novel treatments for asthma? *BJ Pharmacol* 2011;163:81-95; Pettipher R, Hansel TT, Armer R. Antagonism of the prostaglandin D2 receptors DP1 and CRTH2 as an approach to treat allergic diseases. *Nature* 2007;6:313-25; and Schuligoi R, Strum E, Luschnig P, et al. CRTH2 and D-type prostanoid receptor antagonists as novel therapeutic agents for inflammatory diseases. *Pharmacology* 2010;85:372-82.

testing in atopic patients (Keogh, Parker 2011). Of known molds, *Alternaria* provokes symptoms of asthma most routinely (Fernandez 2011). Pets are also allergenic, although if a child has no family history of allergic diseases, pet ownership may be protective. The relationship with a pet is less straightforward in children with family histories of allergic diseases (Lodge 2011). It is postulated that cockroach allergen consists of a combination of cockroach bodies, feces, and saliva-containing proteins and proteases that can disrupt the airway epithelium (Gao 2011).

Exposure to tobacco smoke and air pollution are also linked to the onset of asthma (Flodin 1995). Both active smoking and exposure to secondhand smoke have long been known as triggers of asthma symptoms. The onset of pediatric respiratory illnesses may begin during fetal development. Exposure to tobacco smoke early in life diminishes airway function and decreases lung growth (Stocks 2003). Those reductions cause changes in forced vital capacity (FVC), forced expiratory volume in 1 second (FEV1), and maximal midexpiratory flow. Maternal smoking is linked to infant wheezing (Jindal 2004). The role of air pollution (e.g., nitrogen dioxide, ozone, particulate matter generated by industry and vehicle traffic) in causing asthma is less clear (Takizawa 2011), although exposure to high levels of air pollution is a well-known trigger for exacerbations (Rosenlund 2009) and can also lead to reduction in lung growth (Gauderman 2004) brought on by oxidative stress and carbon accumulation in macrophages (Rosenlund 2009).

### Obesity and Asthma

Obesity may be a possible cause of asthma. During 2009–2010, more than one-third of U.S. adults and about 17% of children were obese (Ogden 2011). With both asthma and obesity increasing in prevalence, an association between the two is being explored. Interpreting the results of asthma and obesity trials can be difficult because objective measures of both asthma diagnoses and weight are not uniform. Confounding biases such as diet and physical activity also vary across studies. Overweight or obesity is not a risk factor for atopy or eosinophilia, suggesting that obesity may affect the airway through mechanisms other than allergic inflammation, such as increased oxidative stress, airways narrowed by chest restriction, and obesity-related comorbidities such as obstructive sleep apnea and gastroesophageal reflux disease (Lang 2012; Lugogo 2010).

## SCREENING AND PREVENTION

### High-risk Population Identification and Management

Asthma is the most common pediatric respiratory disorder that can continue into adulthood. Identification of patients at high risk of exacerbations can improve asthma outcomes and decrease costs by leading to improved asthma care. The Healthcare Effectiveness Data and Information

Set (HEDIS) is an instrument health plans use to gauge quality of care of patients (Box 1-1). Better quality of care of asthma for a particular population (e.g., across members of a health plan) can be assessed by such performance measures as survey data and administrative (pharmacy) data (Schatz 2011). The medication ratio measure is the ratio of controllers to total asthma drugs (controllers plus rescue inhalers) dispensed in a 12-month period. The relationship between a medication ratio of 0.5 or greater and a reduced likelihood of subsequent asthma exacerbations has been established. Also, low scores on three validated questionnaire tools reflect asthma impairment: Asthma Control Test (ACT) score lower than 16, Asthma Quality of Life Questionnaire score of 4.7 or lower, and Asthma Impact Survey score higher than 60 (Schatz 2011). The degree of impairment is not specified, and it should be noted that according to EPR-3, the cutoff value for poorly controlled asthma is an ACT score lower than 19.

Overreliance on quick-acting albuterol can increase the risk of uncontrolled asthma and asthma fatalities (Spitzer 1992). Other risk factors associated with near-fatal exacerbations are nonadherence and poor access to care (Carroll 2010). By applying these criteria to their own patients, providers can better focus attention on patients at highest risk. Pharmacists can assist by informing providers of refill histories and compliance markers and by educating patients on the importance of adherence, on good device technique, and on proper use of quick-acting agents.

### Prevention of Acute Asthma

Acute asthma episodes or exacerbations are random and alarming, and they impair quality of life. Patients can prevent exacerbations by adhering to controller drug regimens and avoiding known triggers. Patients should also be immunized against influenza annually. Those 19 years or older should also receive pneumococcal polysaccharide vaccine.

Most patients with asthma are poor perceivers of asthma control. In a recent study, nearly three-fourths of adolescents rated themselves as having good disease

#### Box 1-1. HEDIS Measures for Identifying High-Risk Patients with Asthma

A patient is considered at high risk if any of the following criteria were met in the past year:

- $\geq 1$  emergency department visit for asthma
- $\geq 1$  hospitalization for asthma
- Use of  $\geq 4$  asthma medication prescriptions
- $\geq 4$  ambulatory visits for asthma with  $\geq 2$  asthma drug prescriptions

HEDIS = Healthcare Effectiveness Data and Information Set. Information from Bennett AV, Lozano P, Richardson LP, et al. Identifying high-risk asthma with utilization data: a revised HEDIS definition. *Am J Manag Care* 2008;150-6. 4:4

control. However, when evidence-based criteria were applied, only 8% actually had good control (Britto 2011). The way that patients with asthma describe symptoms—especially dyspnea—is consistent from age 8 years through adulthood (Harver 2011). Because symptom descriptions are to a large extent universal, pharmacists can help patients develop self-efficacy, especially in recognizing the signs and symptoms of poor control (Box 1-2) and knowing when to seek medical care.

Current guidelines recommend that a patient have a self-management asthma action plan in place to direct both controller and acute symptom treatment. Such plans may include how to adjust reliever and controller drugs, as well as how to minimize and control environmental triggers. Action plans empower patients to handle acute situations while minimizing panic and stressing adherence. As of 2010, all 50 of the United States protect a student's right to carry and self-administer asthma drugs while at school. State legislative requirements are available [online](#), and the [CDC Web site](#) is a resource for action plans.

### Evidence for Prevention with Drug Therapy

To limit the risk of acute exacerbations, providers should urge patients to adhere to controller drugs. Providers should also recommend inhaled corticosteroids (ICSs) over alternatives such as montelukast, theophylline, and nebulized cromolyn. Patients should be treated in a stepwise manner according to their asthma stage at diagnosis or level of control. More information is available in the [EPR-3 guidelines](#).

## DIAGNOSIS AND PROGNOSIS

### EPR-3 Diagnostic Criteria

Criteria for diagnosis of asthma include the presence of episodic signs and reversible airflow obstruction

#### Box 1-2. Signs and Symptoms Indicating Poor Asthma Control

- Shortness of breath or wheezing > 2 days/week
- Nighttime awakenings > 1 day/week
- Some limitation in normal activity
- Use of quick-acting agent > 2 days/week
- FEV1 or peak flow 60% to 80% predicted or personal best
- Score of > 1 on ATAQ,  $\geq 1.5$  on ACQ, or < 19 on ACT QOL questionnaires

ACQ = Asthma Control Questionnaire, ACT = Asthma Control Test, ATAQ = Asthma Therapy Assessment Questionnaire, QOL = quality of life

Information from National Heart, Blood, and Lung Institute. National Asthma Education and Prevention Program. Expert Panel Report 3. Guidelines for the diagnosis and management of asthma. 2007.

and the exclusion of other causes (EPR-3 2007). The guidelines recommend clinicians perform a physical examination and obtain a medical history. Spirometry should be performed in all patients older than 5 years to assess for airway obstruction and reversibility. Reversibility is defined as a change in baseline FEV1 of greater than 200 mL and 12% after inhalation of a short-acting  $\beta$ -agonist (EPR-3 2007). Because histamine and methacholine act directly on smooth muscle cells to cause bronchoconstriction and airway hyperresponsiveness (Sverrild 2010), a bronchial provocation test using histamine or methacholine may be necessary to definitively rule out asthma in patients with normal spirometry who remain symptomatic (Sverrild 2010). Additional tests may be necessary to exclude other diagnoses such as gastroesophageal reflux disease, vocal cord dysfunction, a foreign object in the airway, or a bacterial or viral infection.

The prognosis of asthma is challenging because no absolute indicators are available. However, the persistence of childhood asthma into adulthood can be predicted by the presence of available risk factors (Table 1-1).

## TREATMENT GOALS

Patients, in company with their clinicians, should be encouraged to identify goals of treatment. Engaging a patient in a mutually agreed-upon treatment plan increases patient commitment to both short- and long-term treatment goals. General goals of treatment are to prevent acute and chronic symptoms, maintain normal pulmonary function, minimize adverse drug effects, maintain normal activity levels, and meet the patient and family expectations of care (EPR-3 2007). Clinicians should identify any culture-related beliefs regarding goals of therapy, use open-ended questioning techniques, and involve the family in the decision-making process. More information about the use of motivational interviewing is available [online](#).

## QUALITY PATIENT CARE

### Trigger Avoidance

Patients should learn to recognize their own asthma symptom triggers. The most common triggers are viral or bacterial infections, allergens such as animal dander or pollen, and exposure to tobacco smoke. Others triggers are high levels of air pollution, occupational exposure to chemicals, drugs such as  $\beta$ -blockers, exercising, and food preservatives. If triggers are identified and aversion is discussed, the patient is more likely to avoid the triggers (Rank 2010). Although trigger avoidance usually is discussed during or after an asthma exacerbation, opportunities should be captured in the outpatient setting as well.

**Table 1-1.** Risk Factors for Persistent Asthma

Children younger than 3 years who, in the past year, have experienced four or more episodes of wheezing that lasted more than 1 day and affected sleep are more likely to have persistent asthma after the age of 5 years if they also have:

*One of the following:*

Parental history of asthma

Diagnosed atopic dermatitis

Evidence of sensitization to aeroallergens

*Or two of the following:*

Evidence of sensitization to foods

≥4% peripheral blood eosinophilia

Wheezing apart from colds

Information from National Heart, Blood, and Lung Institute. National Asthma Education and Prevention Program. Expert Panel Report 3. Guidelines for the diagnosis and management of asthma. 2007.

## Environmental Control

Similar to trigger avoidance, controlling the patient's environment could lead to better health outcomes. Reducing environmental triggers in urban-living children can decrease reliance on the emergency department, shorten the length of hospital stays, and reduce the number of sick visits to clinicians because of asthma (Bryant-Stephens 2008). Pharmacists, too, can educate patients to avoid exercise during poor air quality days, to empty trash receptacles often to avoid the presence of cockroaches, and to use mattress encasings that limit dust mite exposure. Pharmacists are well positioned—and should be prepared—to discuss smoking cessation techniques and pharmacotherapies in patients with asthma and their household contacts and how to control exercise-induced bronchoconstriction. More information is available at the Environmental Protection Agency's Web site. Pharmacists can also refer patients with questions related to exercise-induced bronchoconstriction to the American Academy of Allergy Asthma & Immunology Web site.

## RECENT OUTCOMES EVIDENCE

### Pharmacogenomic Testing

The successful mapping of the human genome and advances in pharmacogenomics can help identify genetic markers that influence how humans respond to drugs. In the future, predictive medicine will be commonplace. New tools for assessment and targeted drugs with improved efficacy and limited adverse effects will also become available. To date, pharmacogenomics research in asthma focuses primarily on the use of and response to short-acting  $\beta$ -agonists (SABAs) (Blakey 2011). Albuterol is the most commonly prescribed asthma drug worldwide (Corvol 2008), and determining which patients respond to this agent can potentially improve outcomes. Similarly, excessive SABA use and the use of long-acting  $\beta$ -agonists (LABAs) as monotherapy have been linked to asthma mortality; it is unknown whether this association is caused by genetic variations or the result of uncontrolled inflammation (EPR-3 2007).

The genetic polymorphism with the most data and interest is the  $\beta_2$ -adrenergic receptor (*ADRB2*), which is linked to bronchodilator response (Lima 2009). The *ADRB2* gene is located on chromosome 5q31.32. Two mutations on this gene result in amino acid exchanges at the receptor (arginine 16 to glycine [Arg16 Gly] and glutamine 27 to glutamic acid [Gln 27 Glu]). The changes in those two positions decrease agonist binding and cause down-regulation of the receptor (Finkelstein 2009). Those polymorphisms may also lead to decreased pulmonary function, cause poor bronchodilator responsiveness, and contribute to as much as 60% of variations in response to albuterol (Hizawa 2011). Table 1-2 describes the distribution of  $\beta_2$ -adrenergic receptor alleles in the general population.

Thr-Ile164 is a rare polymorphism (allelic frequency of only 3% in whites) that can alter agonist binding properties and adenylyl cyclase activation. Patients with this polymorphism may experience as much as a 50% decrease in the duration of action of salmeterol because of altered binding to the receptor (Hall 2007).

Although genetic testing is not yet commonplace, pharmacists may be called upon in the future to help patients and prescribers understand genetically driven therapies. Home test kits for the Arg16 polymorphism are available over the Internet; however, the U.S. Food and Drug Administration (FDA) has not approved the labeled use of such kits. More information is still needed to fully understand the role of the *ADRB2* gene, polymorphisms, and the role the *ADRB2* gene plays in  $\beta$ -agonist responsiveness and in asthma itself. Pharmacists should feel confident about continuing to recommend LABAs plus ICSs for patients with moderate to severe persistent asthma. If a genotype is known, however, tailored therapy is appropriate (Figure 1-2).

### Pharmacogenomic Data

#### SABA Data

Most pharmacogenomic studies in patients with asthma focus on the Arg16 polymorphism. Data suggest that patients who are homozygous for Arg16 have a greater initial bronchodilator response to inhaled  $\beta_2$ -agonists;

however, with repeated exposure, these patients demonstrate down-regulation, and a reduced response occurs (Hall 2007). Patients homozygous for Arg16 may be protected against this lack of response to LABA agents by using an ICS (Hall 2007). The consequences of the *ADRB2* gene on  $\beta$ -agonist response may be linked to the duration of therapy. Patients who are homozygous for Arg16 and treated with regular SABAs exhibit lower peak expiratory flow (PEF) than Gly16 homozygous (Gly/Gly) patients. Patients homozygous for Arg16 and mild persistent asthma derive benefit from using ipratropium as a rescue drug. Such patients had worsening symptom scores, reduced lung function, and increased rescue drug use when using salbutamol (albuterol) (Israel 2004).

Contrary to those findings, another study found that albuterol maximally increased FEV1 to a greater extent in patients homozygous for Arg16 compared with a cohort of Gly16 carriers (18% vs. 4.9%,  $p < 0.03$ ) (Lima 1999). To further complicate the debate, a later meta-analysis of trials included children with Arg16 Gly and Gln27 Glu polymorphisms. In children with asthma and the homozygous Arg16 genotype, an association between a favorable therapeutic response to inhaled SABA (odds ratio [OR] 1.77; 95% confidence interval [CI] 1.01–3.1) was reported compared with Arg16/Gly16 (heterozygous Arg16) or homozygous Gly16 genotypes. The beneficial effect of homozygous Arg16 was most pronounced in African American children (OR 3.54; 95% CI 1.37–9.13). No association was found between polymorphisms at position 27 of *ADRB2* and response in children (Finkelstein 2009).

### LABA Data

To determine the effect of long-acting  $\beta$ -agonists in patients with *ADRB2* polymorphisms, the Long-Acting Beta Agonist Response by Genotype (LARGE) trial studied the effect of  $\beta_2$ -adrenergic receptor polymorphism on the response to long-acting  $\beta_2$ -agonist in asthma. The

cohort included patients who were homozygous to either Arg16 or Gly16. The mean morning PEF in the homozygous Arg16 subjects was 21.4 L/minute greater in the salmeterol group than in the placebo group ( $p < 0.0001$ ). Similarly, patients with homozygous Gly16 had morning PEFs that were 21.5 L/minute greater when assigned to salmeterol versus placebo ( $p < 0.0001$ ). Neither genotype had a specific advantage for ipratropium versus salbutamol. The authors concluded that homozygous Arg16 and homozygous Gly16 patients with asthma had similar—and substantial—improvements in airway function when salmeterol was added to ICS therapy (Wechsler 2009).

That same year, another group studied the effect of *ADRB2* polymorphism on asthma control in Korean patients receiving combination therapy. The cohort included patients with Arg/Arg, Arg/Gly, and Gly/Gly polymorphisms. During the 24-week active treatment phase, patients were started on budesonide 160 mcg and formoterol 4.5 mcg twice daily. After 8 weeks, the patients with the Arg/Arg genotype had significantly higher FEV1 and maximal midexpiratory flow than did those with the Arg/Gly or Gly/Gly genotype ( $p < 0.05$ ). After 24 weeks, the patients with the Arg/Arg genotype had a significantly higher quality of life than the Arg/Gly or Gly/Gly group ( $p < 0.05$ ). Such results demonstrate that combination ICSs and LABAs as maintenance therapy would have more benefit for patients with the Arg/Arg genotype than patients with the other genotypes. This is not consistent with previous studies in white subjects (Kim 2009).

Patient response to corticosteroids also may be linked to pharmacogenomics. The anti-inflammatory properties of corticosteroids are enhanced by *ADRB2* activation. That theoretical mechanism explains the synergy seen between *ADRB2* and glucocorticoid receptor activation. Binding to the *ADRB2* receptor also leads to desensitization and down-regulation through a negative feedback loop. The clinical manifestation is tachyphylaxis with *ADRB2*-agonist therapy (Chung 2011). In vitro studies show glucocorticosteroids prevent and reverse the desensitization caused by chronic exposure to  $\beta$ -agonists (Tse 2011). Greater down-regulation of receptors was reported in those homozygous for the Gly16 genotype than in those homozygous for Arg16. That down-regulation of receptors in patients with Glu27 genotype is less compared with those with the Gln27 genotype (Chung 2011), thereby helping predict possible tachyphylaxis with continued SABA therapy (see Figure 1-2).

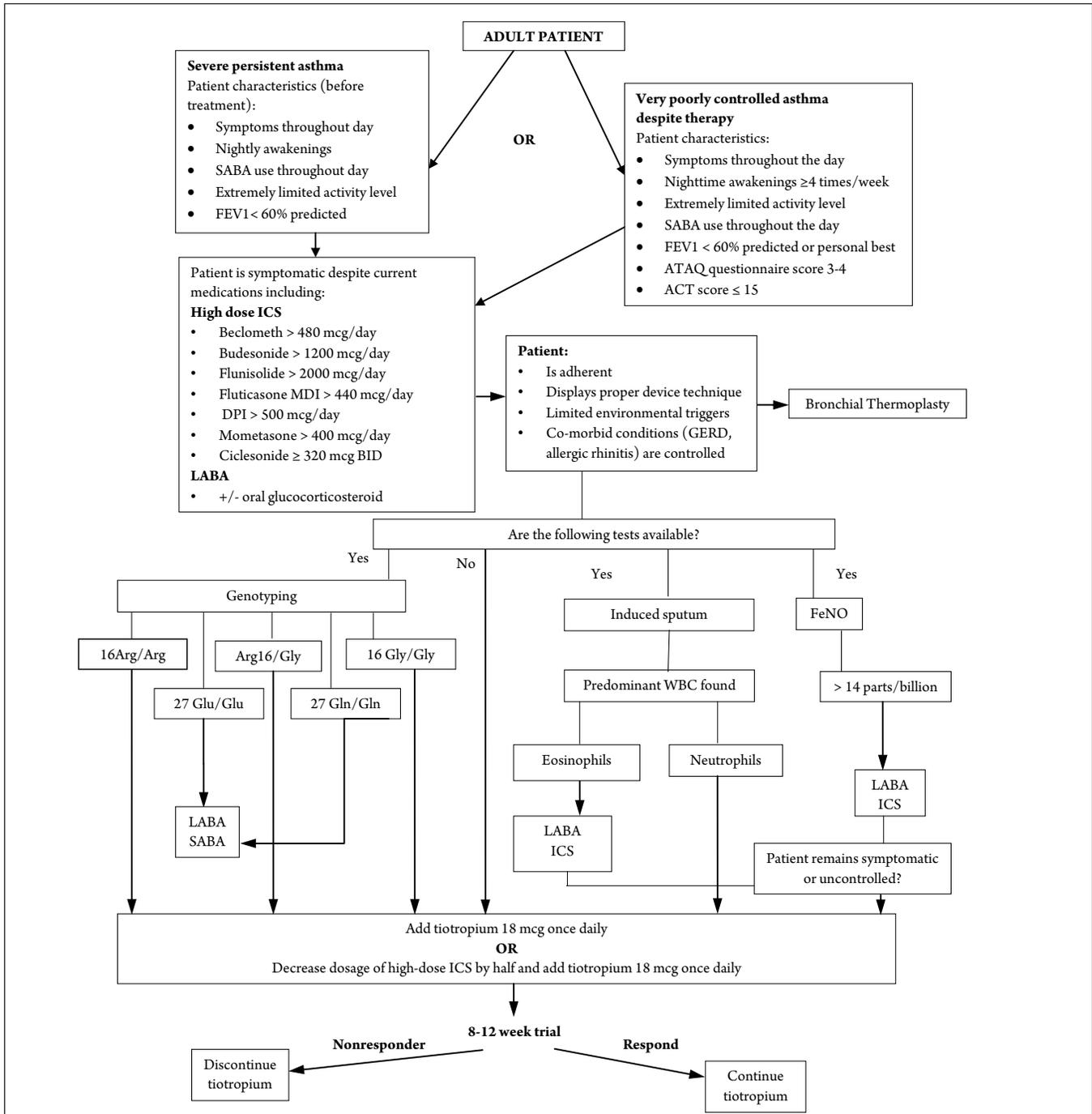
### Pharmacogenomic Summary

Pharmacists may be asked to help patients understand genetically driven therapies. Genetic testing is increasingly available. A home test kit, currently on the market for around \$300, uses the DNA obtained from a cheek swab sample to assess for the Arg/Arg polymorphism in the *ADRB2* gene. Such information may benefit patients by allowing treatment plans to be based on evidence

**Table 1-2.** Distribution of  $\beta_2$ -Adrenergic Receptor Alleles in the General Population

Allele	Description	Proportion
Arg16/Arg16	Homozygous Arg16	15%
Arg16/Gly16	Heterozygous Arg 16	38%
Gly16/Gly16	Homozygous Gly16	45%
Gly27/Gly27	Homozygous Gly27	26%
Gln27/Glu27	Heterozygous Gln27	49%
Glu27/Glu27	Homozygous Glu27	22%

Information from Lima JJ, Thomason DB, Mohamed MHN, et al. Impact of genetic polymorphisms of the  $\beta_2$ -adrenergic receptor on albuterol bronchodilator pharmacodynamics. *Clin Pharm Ther* 1999;65:519-25.



**Figure 1-2.** Decision tree for the patient with asthma.

FEV = forced expiratory volume; FEV1 = forced expiratory volume in 1 second; ICS = inhaled corticosteroid; LABA = long-acting  $\beta$ -agonist; SABA = short-acting  $\beta$ -agonist.

Information from Bateman ED, Kornmann O, Schmidt P, et al. Tiotropium is noninferior to salmeterol in maintaining improved lung function in  $\beta 16$ -ARG/ARG patients with asthma. *J Allergy Clin Immunol* 2011;128:315-22; Fardon T, Haggart K, Lee DKC, et al. A proof of concept study to evaluate stepping down the dose of fluticasone in combination with salmeterol and tiotropium in severe persistent asthma. *Respir Med* 2007;101:1218-29; Iwamoto H, Yokoyama A, Shiota N., et al. Tiotropium bromide is effective for severe asthma with noneosinophiic phenotype. *Eur Respir J* 2008;31:1379-82; Kerstjens HA, Disse B, Schroder-Babo W, et al. Tiotropium improves lung function in patients with severe uncontrolled asthma: a randomized controlled trial. *J All Clin Immunol* 2011 128:308-14; Kerstjens HA, Engel M, Dahl R, et al. Tiotropium in asthma poorly controlled with standard combination therapy. *N Engl J Med* 2012;367:1198-207; Park HW, Yang MS, Park CS, et al. Additive role of tiotropium in severe asthmatics and Arg16Gly in ADRB2 as a potential marker to predict response. *Allergy* 2009;64:778-83; and Peters SP, Kunselman SJ, Icitovic N, et al. Tiotropium bromide step up therapy for adults with uncontrolled asthma. *N Engl J Med* 2010;363:1715-26.

regarding their genotype. More information is still needed to fully understand the role of the *ADRB2* gene, of polymorphisms, and of the gene's role in both  $\beta$ -agonist responsiveness and asthma itself.

### Role of Tiotropium for Asthma

The use of anticholinergic drugs in patients with asthma has been relegated primarily to the acute setting. The use of ipratropium results in fewer hospitalizations if given in combination with a SABA to patients experiencing exacerbations in the emergency department (EPR-3 2007). The use of anticholinergic drugs in asthma is fitting. Acetylcholine, a parasympathetic neurotransmitter, stimulates muscarinic receptors; this results in smooth muscle contraction, release of mucus from submucosal glands, airway inflammation, and airway remodeling (Gosens 2006). Cholinergic tone can also become exaggerated when stimulated by inflammatory mediators such as histamine, prostaglandins, and bradykinin. Other mechanisms that may increase cholinergic tone in airways include increased release of acetylcholine from cholinergic nerve terminals, abnormal muscarinic receptor expression (increase in M3, decrease in M2), and a decrease in neuromodulators such as nitric oxide and intestinal peptide (Kanazawa 2008).

As previously mentioned, patients who are homozygous for Arg16 may not respond to  $\beta_2$ -agonists (Metzger

2008). African American and Asian populations have an increased prevalence of the Arg16 genotype, and the use of alternative controllers and rescue inhalers other than LABAs and SABAs may be appropriate. One study found that tiotropium had a prolonged bronchodilating effect and provided protection against inhaled methacholine in patients with asthma (O'Connor 1996). In a later study, asthma patients received high-dose fluticasone that was stepped down to a one-half dose with either salmeterol and placebo or salmeterol and tiotropium. The authors found that the triple-drug therapy (ICS dose decreased by half plus salmeterol and tiotropium) resulted in a statistically significant mean improvement in FEV1 and FVC (Fardon 2007) (Table 1-3).

In 2008, another team investigated the efficacy of tiotropium in 17 patients with severe asthma taking 800–1600 mcg daily of budesonide or equivalent. The authors found that the more eosinophils in the sputum, the less likely it was that the patient would respond to tiotropium. The opposite was true for patients with a majority of sputum neutrophils. Patients on medium to high doses of ICSs with noneosinophilic sputum profiles had better responses to tiotropium, which is not surprising given the value of tiotropium in patients with chronic obstructive pulmonary disease when neutrophilic inflammation is widespread (Iwamoto 2008).

**Table 1-3.** Stepping Down Fluticasone in Severe Persistent Asthma

Mean peak flow rates 4 weeks after treatment			
Treatment	Fluticasone 1000 mcg/day	Fluticasone 500 mcg/day Salmeterol 50 mcg twice daily Placebo	Fluticasone 500 mcg/day Salmeterol 50 mcg twice daily Tiotropium 18 mcg daily
Morning PEF	-	41.5 (14.4-68.6) L/minute (p<0.01)	55.3 (31.97-78.7) L/min (p<0.01)
Evening PEF	-	37 (12-63) L/minute	44 (26-62) L/minute
Mean lung function values (SEM)			
Treatment	Fluticasone 1000 mcg/day	Fluticasone 500 mcg/day Salmeterol 50 mcg twice daily Placebo	Fluticasone 500 mcg/day Salmeterol 50 mcg twice daily Tiotropium 18 mcg daily
FEV1 (L)	1.62 (0.14)	1.73 (0.12)	1.79 (0.12) <sup>a</sup>
FEV1 (%)	55 (2.9)	60 (3.1)	62 (2.9) <sup>a</sup>
FVC (L)	2.44 (0.2)	2.57 (0.19)	2.68 (0.19) <sup>a</sup>
FVC (%)	68 (3.6)	72 (3.1)	75 (2.8) <sup>a</sup>

<sup>a</sup>Statistically significant.

FEV1 = forced expiratory volume at 1 second, FVC = forced vital capacity, PEF = peak expiratory flow

Information from Fardon T, Haggart K, Lee DKC, et al. A proof of concept study to evaluate stepping down the dose of fluticasone in combination with salmeterol and tiotropium in severe persistent asthma. *Respir Med* 2007;101:1218-29.

The best-known trial on the use of tiotropium in patients with asthma was conducted for the Asthma Clinical Research Network and sponsored by the National Heart, Lung, and Blood Institute. The study evaluated whether adding tiotropium to an ICS would be superior to doubling the dose of the ICS. The three-way, double-blind, triple-dummy, crossover-designed trial enrolled patients with mild asthma not controlled by an ICS. After a 4-week run-in period, all patients were given beclomethasone 80 mcg twice daily. Weeks 3 and 4 of the run-in period provided baseline data. The treatment phase then consisted of 14 weeks with beclomethasone 80 mcg twice daily plus tiotropium 18 mcg once daily, or beclomethasone 160 mcg twice daily, or beclomethasone 80 mcg plus salmeterol 50 mcg twice daily. Between each phase was a 2-week washout period during which patients were given beclomethasone. Patients receiving beclomethasone plus tiotropium had a higher morning PEF than patients on doubled-dose ICS (25.8 L/minute more,  $p < 0.001$ ). Tiotropium was also better with respect to evening PEF (difference of 35.3 L/minute,  $p < 0.001$ ), prebronchodilator FEV1 (difference of 0.1 L,  $p = 0.004$ ), proportion of asthma-control days (difference of 0.079,  $p = 0.01$ ), daily symptom scores (difference of  $-0.11$  points,  $p < 0.001$ ), and FEV1 after four puffs of albuterol (difference of 0.11 L,  $p = 0.003$ ) than in patients on doubled-dose ICS. Tiotropium was superior to doubling of the ICS dosage for patients whose symptoms were inadequately controlled while receiving beclomethasone alone at a dosage of 80 mcg twice daily (Peters 2010). Similarly, patients not controlled on high dosages of ICS plus LABA had either tiotropium or placebo added, the mean FEV1 peak was significantly higher with both tiotropium dosages than with placebo (difference of 5 mcg, 0.139 L,  $p < 0.001$ ), and 10 mcg, 0.170 L,  $p < 0.001$ ) (Kerstjens 2011). Both 5 mcg and 10 mcg of tiotropium delivered by the Respimat Soft Mist device are equivalent to 18 mcg delivered by the HandiHaler (Caillaud 2007).

A similar trial investigated the long-term safety and efficacy of adding tiotropium (5 mcg by the soft-mist inhaler) to patients on high-dose ICS plus LABA. Two replicate randomized, double-blind, placebo-controlled, parallel-group trials were conducted over a 48-week period. The primary outcomes were FEV1 and length of time to first severe asthma exacerbation. At 24 weeks, the mean difference in peak FEV1 between the tiotropium group and the placebo group was 86  $\pm$  34 mL in trial 1 ( $p = 0.01$ ) and 154  $\pm$  32 mL in trial 2 ( $p < 0.001$ ). The between-group difference in change from baseline trough FEV1 at 24 weeks was also significantly greater in the tiotropium group versus placebo (88  $\pm$  31 mL in trial 1,  $p = 0.01$ , and 111  $\pm$  30 mL in trial 2,  $p < 0.001$ ). The time to first exacerbation was increased by 56 days in the tiotropium group over the placebo group (282 days vs. 226 days), which corresponded to a reduction of 21% in risk (hazard ratio 0.79; 95% CI 0.62–1.00;  $p = 0.03$ ). This group of trials showed that tiotropium added sustained bronchodilation over

24 hours and reduced severe exacerbations in patients with asthma who had been symptomatic with persistent airflow limitation despite the use of high-dose ICS plus LABA (Kerstjens, 2012).

Given the effect of genetic polymorphisms on  $\beta$ -agonist failure, alternatives to  $\beta$ -agonists are being investigated. One trial investigated patients with homozygous Arg16 moderate persistent asthma who were receiving ICS (400–1000 mcg of budesonide or equivalent per day). Patients were randomized to one of three arms: tiotropium 5 mcg daily plus salmeterol placebo device; salmeterol metered-dose inhaler 25 mcg two puffs twice daily plus tiotropium placebo device; or placebo. Mean weekly morning predose PEF was maintained during the treatment period with tiotropium and salmeterol but decreased for those on placebo. Tiotropium was noninferior to salmeterol (tiotropium minus salmeterol estimated difference:  $-0.78$ ; 95% CI  $-13.096$  to  $11.53$ ,  $p = 0.02$ ), and both tiotropium and salmeterol were superior to placebo (Bateman 2011). Correspondingly, a 2009 trial examined the impact of the addition of tiotropium on improved lung function in patients with severe asthma. The investigators also sought to identify factors capable of predicting a response to tiotropium by taking a pharmacogenetic approach. Targeted genes were *CHRM1*, *CHRM2*, and *CHRM3* (which code for muscarinic receptors 1 to 3), and *ADRB2*. The Arg16Gly polymorphism was significantly associated with response to tiotropium (Park 2009).

Tiotropium can be recommended for patients with severe persistent asthma who continue to be symptomatic on high dosages of ICS and LABA (see Figure 1-2). Genetic testing is not occurring extensively in clinical practice because of cost and lack of routine insurance coverage for such services. When genetic testing or sputum induction studies are available, the results can further guide decision-making with regard to tiotropium. If a patient's asthma does not respond as assessed by symptom scores, quality-of-life measures, or pulmonary function after an 8- to 12-week trial, tiotropium should be discontinued.

### Differences in Inhalers

Since 2009, only albuterol hydrofluoroalkane (HFA) metered-dose inhalers are permitted in the United States. The HFA albuterol inhaler delivers a dose of albuterol (90 mcg per puff) comparable to that of the older chlorofluorocarbon inhalers. Patients may notice a different taste and feel, because HFA inhalers emit a dose that uses less force and has a smaller plume (Hendeles 2007).

Some differences exist between the three available HFA albuterol inhalers (Table 1-4). Ventolin HFA contains only the drug and the propellant, which may lead to better tolerability in some patients (Hendeles 2007). Also, excipients added to ProAir HFA and Proventil HFA differ, making the three products not interchangeable (BX rated) (Orange Book 2012). Differences in spray characteristics also influence patient reactions. A metered-dose inhaler

with a higher force may cause increased throat deposition, whereas a lower spray temperature may cause a *cold-Freon effect*. In both instances, the patient might stop inhaling prematurely (Gabrio 1999). The cold-Freon effect was common with the older chlorofluorocarbon inhalers, but some data to suggest it may also occur with the HFA inhalers.

One study collected the temperatures of emitted plumes, the maximum compressive force, and the aerodynamic-particle-size distribution of ProAir HFA and Ventolin HFA. The mean minimum plume temperatures were significantly higher for ProAir HFA (7.2 +/- 0.7°C) compared with Ventolin HFA (-35.9 +/- 12.7°C, p=0.0001). ProAir HFA produced a plume duration that lasted 2.5 times longer than that of Ventolin HFA (385 +/- 46 microseconds vs. 156 +/- 58 microseconds, p=0.0001). Also, the spray force of ProAir HFA was 55% lower than that of Ventolin HFA (33.6 +/- 11.4 milli-Newton vs. 75.9 +/- 12 milli-Newton, respectively, p=0.0001). The ProAir HFA product produced almost twice as many fine particles as did the Ventolin HFA inhaler (53 +/- 4 mcg vs. 26 +/- 2 mcg) (McCabe 2012).

The favorable spray characteristics of ProAir HFA (e.g., longer duration, lower impact, warmer plume, higher number of fine particles) decrease the chances of the cold-Freon effect. Additional studies comparing the pre- and

postbronchodilator FEV1 readings of the three different HFA albuterol products would be useful for clinicians. A switch to ProAir HFA may be warranted for patients who experience the cold-Freon effect or who are unable to use albuterol because of other negative spray characteristics.

### New Directions in Asthma Assessment

Recent research has focused on the signaling molecule, nitric oxide (NO), which is found in car exhaust emissions and acid rain and which can deplete the ozone layer. In the lung, this chemical acts as a vasodilator, a bronchodilator, a nonadrenergic noncholinergic neurotransmitter, and an agent of inflammation. Chemiluminescence can detect exhaled NO; when a sample is mixed with ozone, a chemical reaction produces oxygen and nitrogen dioxide with the emission of light. The amount of light measured by the photodetector is proportional to the amount of NO in the sample. Normal concentrations are 8 to 14 parts per billion (Yates 2001).

The fraction of exhaled NO may be an indicator of eosinophilic inflammation in the airway. If the fraction is high, patients are more likely to respond to ICS (Munakata 2012). Values greater than 50 parts per billion in adults and greater than 35 parts per billion in children can be used to indicate eosinophilic inflammation (Dweik 2011). Conversely, values less than 25 parts per billion

**Table 1-4.** Differences in HFA Albuterol MDI Characteristics

	ProAir HFA	Proventil HFA	Ventolin HFA	Xopenex HFA
Number of actuations to prime inhaler	3	4	4	4
When to prime	First-time use, not used for >2 weeks	First-time use, not used for >2 weeks	First-time use, not used for >2 weeks or when the inhaler has been dropped	First-time use, not used for >3 days
Protective pouch required before dispensing?	No	No	Yes	No
Cleaning	Wash weekly with warm water; air dry			
Expiration date	2 years	After all actuations have been used	6 months after removal from pouch	After all actuations have been used
Proper storage position	Any position	Any position	Upright position (mouthpiece down)	Upright position (mouthpiece down)
Plume temperature (°C)	7.2 +/- 0.7	N/A	-35.9 +/- 12.7	N/A

HFA = hydrofluoroalkane; MDI = metered-dose inhaler.

Information from manufacturer package inserts and McCabe JC, Koppenhagen F, Blair J, et al. ProAir HFA delivers warmer, lower-impact, longer-duration plumes containing higher fine particle dose than Ventolin HFA. *J Aero Med Pulm Drug Del* 2012;25:104-9.

in adults and less than 20 parts per billion in children should be interpreted as low; therefore, responsiveness to corticosteroids is less likely.

The tools to measure exhaled NO have yet to be standardized, and large population studies are needed to determine the effect of confounding biases (Dweik 2011). Therefore, routine tailoring of interventions based on NO cannot be recommended at this time (Petsky 2009). Providers can use the fraction of exhaled NO as an adjunctive tool when assessing patients with asthma. Also, if patients report adherence to an ICS, yet their exhaled NO readings remain high, further investigation on symptoms and adherence may be warranted. The [American Thoracic Society's position on exhaled NO](#) is available online.

### Impulse Oscillometry

Impulse oscillometry is a forced oscillation technique that can be used for diagnostic purposes when spirometry is not an option, such as in the frail elderly and in young children (Tanaka 2011). The technique is delivered through an apparatus applied at the mouth. The apparatus creates a wave of pressure (oscillation) that gets transmitted into the lungs. The impulse oscillometry evaluates both respiratory resistance (i.e., the energy required to propagate the pressure wave through the airways) and reactance (i.e., the amount of recoil generated against the pressure wave at different oscillatory frequencies) (Komarow 2011). Use of the technique is gaining momentum in diagnosis, evaluation of disease severity, and assessment of response to drug therapy. The results of the noninvasive and rapid technique can be correlated with FEV<sub>1</sub>, FVC, and PEF (Song 2008), but spirometry measures maximal forced respiratory efforts, and forced oscillation measures quiet breathing. If the results of these tests are not closely correlated, it does not imply that the oscillation measurements are not valid (Smith 2005).

## RECENT DEVELOPMENTS IN PHARMACOTHERAPY

### New Labeling Requirements for LABAs

Results of the Salmeterol Multicenter Asthma Research Trial (SMART) showed that at baseline, the enrolled patients had been on standard asthma therapy—including ICS (47% of whites, 38% of African Americans), theophylline, leukotriene modifiers, or inhaled or oral  $\beta$ -agonists (excluding salmeterol)—and randomized to either salmeterol twice daily or placebo. That landmark trial showed an increase in the number of respiratory- and asthma-related deaths in the salmeterol group (13 out of 13,176 patients) compared with the placebo group (3 out of 13,179 patients), with a relative risk of 4.37 (95% CI, 1.25–15.34,  $p < 0.05$ ). A subgroup analysis revealed that the risk may be greater in African American patients compared with whites (Nelson 2006).

The FDA [conducted a meta-analysis](#) to investigate these findings further, finding that LABAs increased the risk of severe exacerbations driven by the number of asthma-related hospitalizations, especially in children aged 4 to 11 years. The result was labeling changes to LABAs. To ensure safe use, clinicians should recognize that LABAs are contraindicated without a controller drug such as an ICS and should be used chronically and long term only if the patient's asthma is not otherwise controlled. In addition, LABAs should be used for the shortest duration possible, and their use in pediatric and adolescent patients is restricted to the form of a combination product.

### The Controversy Involving Long-Term LABA Use

The FDA's 2008 review of the benefits and risks associated with the use of LABAs to treat patients with asthma concluded that the benefits outweigh the risks, and therefore the drugs continued on the market. However, strict label changes were enforced. Long-term use of LABAs is appropriate only for patients whose asthma cannot be managed without them (e.g., patients unable to remain controlled on ICS monotherapy) (Kramer 2009). That view differs from that of the National Asthma Education and Prevention Program's expert panel, as well as many practicing clinicians who advocate reduction in ICS dose of 25% to 50% over 3 months to the lowest dose possible required (Chowdhury 2010; EPR-3 2007). Also, a recent meta-analysis showed that in trials in which LABA therapy was discontinued in patients controlled on LABA plus ICS, the LABA step-off approach resulted in increased asthma impairment, worsening of asthma quality of life questionnaire scores, and fewer symptom-free days (Brozek 2012).

Pharmacists should encourage appropriate use of LABA agents, being careful not to restrict their use for patients who may derive benefit. The FDA mandated a long-term safety study of LABA agents, and this trial is ongoing. The results may help clarify this issue regarding prescribing and recommending LABA agents.

### Step-Up Therapy for Pediatric Patients

There are limited data to guide practitioners' decision-making when pediatric patients remain symptomatic on low-dose ICS. The Best Add-on Therapy Giving Effective Responses trial was a randomized, double-blind, three-treatment, three-period crossover trial for a total of 48 weeks (Lemanske 2010). During each 16-week period, subjects received either 250 mcg fluticasone twice daily, or 100 mcg fluticasone plus 50 mcg salmeterol twice daily, or 100 mcg of fluticasone plus 5 mg or 10 mg of montelukast daily. The authors found that the response to LABA step-up was significantly more likely to be the best response compared with montelukast (relative probability 1.6; 95% CI 1.1–2.3,  $p = 0.004$ ) and the response to ICS step-up (relative probability 1.7; 95% CI 1.2–2.4,  $p = 0.002$ ). Similarly, researchers investigated the combination of salmeterol

and fluticasone versus doubling the dose of fluticasone in pediatric patients with asthma (Vaessen-Verberne 2010). Those authors found that the addition of salmeterol to medium-dose fluticasone was not inferior to doubling the dose of ICS with regard to symptoms during 6 months of treatment.

There have been concerns that the use of LABAs in children may lead to increased risk of exacerbations. However, a Cochrane analysis concluded that adding LABAs did not increase exacerbations requiring oral steroids or hospitalizations when compared with ICS alone.

### Using LABA/ICS Combination Products as Both Reliever and Controller

The concept of using either a device for single maintenance and reliever therapy (SMART) or adjustable maintenance dosing is not new. Studies have shown that formoterol can be an effective reliever agent (Barnes 2007) because of its rapid onset of effect (within 1 minute to 3 minutes) and its long duration of action (12 hours or more) (McCormack 2007). Formoterol causes systemic adverse effects for approximately the same duration as SABAs, which allows for cumulative doses of this drug to be given (Barnes 2007). A real-life study was performed in a diverse population of more than 18,000 patients. This investigator found that using formoterol as a reliever drug was as safe as using a SABA, and it resulted in both prolonged time to a first asthma exacerbation and reduced drug requirements (Pauwels 2003).

The theoretical benefit of combination products is to combine the bronchodilating effects of  $\beta$ -agonists with the anti-inflammatory properties of ICSs when acute therapy is warranted. By intervening early during the time that patients experience debilitating symptoms and deteriorating lung function, severe exacerbations may be prevented (D'Urzo 2006). Study investigators hypothesized that patients on low-dose budesonide/formoterol combination could also use a SMART device for delivery of their quick-relief drug. Such use would enable patients to simultaneously obtain effective and rapid relief from symptoms and adjust their anti-inflammatory therapy at times of greatest need (O'Byrne 2005). That study was groundbreaking because it demonstrated that the budesonide/formoterol combination for both maintenance and quick relief significantly reduced total severe exacerbations, avoided exposure to oral corticosteroids, reduced reliever-drug use, and relieved nighttime symptoms, including awakenings, and mild exacerbation days when compared with budesonide/formoterol or high-dose budesonide for maintenance (both with SABA for quick-relief use) (O'Byrne 2005). The concept has been validated by several other studies. Under the SMART approach, patients had decreased rates of severe exacerbations and associated medical care (Kuna 2007; Rabe 2006a; Rabe 2006b). Similarly, in an open-label trial of 908 patients, SMART was found to be at least as effective

at improving asthma control as conventional practice. The investigators also found SMART resulted in both lower overall ICS dose (a reduction by approximately 300 mcg/day of budesonide equivalents) and significantly lower drug costs (by 25%) (Louis 2009).

Adverse effects most commonly seen with the budesonide/formoterol combination in SMART trials included respiratory tract infection, pharyngitis, rhinitis, bronchitis, sinusitis, headache, and aggravated asthma (McCormack 2007); these were comparable with rates seen when used conventionally (McGavin 2001). The incidence of predictable adverse events—including palpitations, tachycardia, candidiasis, dysphonia, and hoarseness—were low (ranging from 0%–2%).

Neither formoterol nor the formoterol/budesonide combination has FDA label approval for use in the treatment of acute symptoms. The practice of using combination products as both maintenance and reliever therapy is neither routine in the United States nor mentioned in EPR-3; however, it is an option, according to the [Global Initiative for Asthma](#) guidelines. It is an interesting and promising concept because using the same device for both maintenance and acute symptoms is convenient and could decrease device burden. Despite the aforementioned benefits of SMART, however, recommendation of this practice is problematic. First, even though cost savings were seen with SMART, direct costs decreased; drug utilization costs did not. Insurance and pharmacy benefit providers would need to shift their current practice and begin providing more than 1-month supplies of these expensive agents. Second, this practice is based on evidence gained through randomized controlled trials that were conducted at both generalist and specialist offices, where patients were closely monitored but whose locations were outside the United States. Making the leap from randomized controlled trial to clinical practice can be challenging because both the providers and the patients may be skeptical. Last, primary care providers may be more comfortable waiting until a recommendation to utilize SMART is addressed in the next EPR update.

### Treating Small Airway Disease

Asthma is an inflammatory disease that affects the respiratory tract; it extends to the peripheral airways that are less than 2 mm in diameter (sometimes referred to as the small airways). When small airway disease is suspected, the studies that commonly assess airflow measure forced expiratory flow rates at 50% of vital capacity ( $FEF_{50\%}$ ) and at 25% to 75% of vital capacity ( $FEF_{25\%-75\%}$ ). Airway resistance, too, can be measured by impulse oscillometry. Peripheral airway inflammation can also be assessed by the fractional excretion of NO (van den Berge 2011).

Newer inhalation devices enable drugs to better target those small airways. The newer HFA devices generate smaller particles, with an average size of 1 micrometer.

Examples of HFA ICSs are beclomethasone, flunisolide, and ciclesonide. These small-particle HFA metered-dose inhalers result in higher lung deposition compared with conventional dry powder inhalers (50% to 60% vs. 10% to 20%) and lower oropharyngeal deposition (30% to 40% vs. more than 80%) (van den Berge 2011). Typical ICS formulations (fluticasone, beclomethasone, and budesonide) deliver relatively large particles (more than 3 micrometers) that do not penetrate into the small airways (Johnson 2012). Systemic adverse effects of the HFA formulations compared with their chlorofluorocarbon (CFC) or dry powder inhaler counterparts vary. No decrease in either urinary or serum cortisol levels were found with HFA beclomethasone compared with CFC beclomethasone (van den Berge 2011). However, small studies have shown differences in growth velocity between HFA and CFC budesonide in favor of the CFC formulation in children (Gentile 2010). These small-particle ICS agents are equally as effective as the conventional dry powder inhaler agents. For example, results of comparative clinical trials demonstrated that HFA beclomethasone is equivalent to fluticasone (a more potent corticosteroid) at the same dose in maintaining asthma control (Gentile 2010). Further efficacy and safety studies are needed to confirm the advantages of these small-particle ICS agents. In particular, long-term prospective trials evaluating patients with uncontrolled disease despite adherence to a large-particle ICS agent would be helpful.

### **Risks with Omalizumab**

#### **Anaphylaxis**

Omalizumab, a 95% humanized monoclonal antibody that binds to circulating IgE, is currently approved for moderate to severe persistent allergic asthma and for those patients not well controlled on combination medium dosages of ICS and LABA. A boxed warning related to anaphylaxis has been added, and patients should be observed in the clinician's office for 2 hours after each of the first three injections and for 30 minutes after each subsequent dose, because 75% of reported anaphylaxis cases occurred within those periods (Cox 2009). The risk evaluation and mitigation strategy program for omalizumab was discontinued in 2011; however, a [patient medication guide](#) is still required. Patients should have access to self-injectable epinephrine and be educated on the signs and symptoms of anaphylaxis and on the administration of self-injectable epinephrine.

#### **Atherothrombotic Events**

A link between omalizumab use and arterial thrombotic events reported to the FDA Adverse Event Reporting System has been investigated. Myocardial infarction and stroke accounted for the majority of the events. In light of the findings, future robust epidemiologic studies are needed to evaluate that potential, adverse effect (Ali 2011). Until such evidence is available, clinicians should

recommend omalizumab cautiously in patients with known factors that put them at risk of myocardial infarction or stroke.

### **Leukotriene Modifiers and Suicide**

In 2008, the FDA investigated a possible association between the use of montelukast and suicide or suicidal behavior. In 2009, the package inserts for montelukast, zafirlukast, and zileuton were updated to [include neuropsychiatric events](#). A population-based cohort study of patients exposed to one or more prescriptions for montelukast from 1998 to 2007 revealed that among 23,500 patients, one case of suicide occurred in a 61-year-old woman. The patient had been given one prescription for montelukast 2 years before her death, and montelukast was ruled out as the cause (Jick 2009). Other investigators have also been unable to link montelukast to suicide risk (Schumock 2012; Schumock 2011). When prescribing leukotriene modifiers, clinicians are urged not to withhold warranted therapy but to monitor patients for neuropsychiatric effects.

## **EMERGING THERAPIES**

### **Bronchial Thermoplasty**

Bronchial thermoplasty involves the distribution of radio frequency energy into the airways by flexible bronchoscopy to reduce airway smooth muscle mass and decrease bronchoconstriction (Thomason 2011; Wahidi 2011). The electrical energy is delivered through electrodes and is then converted to heat when it comes in contact with tissue (Wahidi 2011). Thermal energy is delivered to the airway wall in a series of three bronchoscopies that take place 3 weeks apart: The first procedure treats the airways of the right lower lobe; the second, the airways of the left lower lobe; and the third, the airways of both upper lobes (Duhamel 2010). When heat is introduced to the smooth muscle of the airway, actin-myosin interaction is disrupted from denaturation of motor proteins, thereby quickly inactivating muscle cells (Gildea 2011).

In 2010, the bronchial thermoplasty received label approval for use in the treatment of patients 18 years or older with severe persistent asthma not well controlled with ICS and LABA (Wahidi 2011). The FDA is requiring phase 4 postmarketing surveillance studies. This therapy is not currently covered by most private insurance plans, which limits its clinical acceptance. Once that barrier has been overcome, interventional pulmonologists as well as bronchoscopists' advanced skills, training, and expertise will be needed for this newly approved technique.

Targeting airway smooth muscle with bronchial thermoplasty is logical because of bronchial thermoplasty's role in bronchoconstriction, promotion of inflammation and airway remodeling, and the expelling of mucus from the lungs. The Asthma Intervention Research (AIR)

trial study group randomized patients to either bronchial thermoplasty or control. The mean number of mild exacerbations was 0.18 +/- 0.31 per subject per week in the bronchial thermoplasty arm 12 months after treatment, compared with 0.35 +/- 0.32 at baseline. The number of mild exacerbations in the control group was 0.31 +/- 0.46 per subject per week compared with 0.28 +/- 0.31 from baseline. The difference between the two groups was significant at months 3 (p=0.03) and 12 (p=0.03). Patients who received bronchial thermoplasty had 10 fewer mild exacerbations per subject per year. If treated with ICS monotherapy, the patients receiving bronchial thermoplasty had a further reduced rate of mild exacerbations (Cox 2007).

Similarly, the Research in Severe Asthma (RISA) study group (Pavord 2007) investigated patients with severe asthma. Bronchial thermoplasty was associated with a short-term increase in morbidity (e.g., worsening asthma symptoms, increased rescue medication use, decreased quality of life and asthma control) in the period immediately after treatment. The use of rescue drugs improved lung function and asthma-related quality of life scores, which remained statistically significant up to 52 weeks after treatment (Pavord 2007). When analyzed together, the results of the AIR and RISA trials indicate that the numbers of adverse events were similar across studies but were worse in patients with more severe disease. Adverse events reported included wheeze, breathlessness, chest tightness, cough, dyspnea, asthma exacerbation, and episodes of lobar segmental collapse. The authors did not, however, show any deterioration in lung function over 3 years, and CT scans showed no evidence of abnormal airway structure or injury to lung tissue (Cox 2009).

In a sham-controlled trial, bronchial thermoplasty led to improvements in severe exacerbations that would have required corticosteroids, emergency department visits, and time lost from work or school during the time after receiving bronchial thermoplasty (Castro 2010). Similarly, a trial assessed the safety of bronchial thermoplasty 5 years after treatment and found that neither the rate of oral corticosteroid usage nor the proportion of subjects requiring oral corticosteroid pulses therapy showed any worsening over the period in the bronchial thermoplasty group. In the bronchial thermoplasty group, 57% reported decreases in LABA usage over those 5 years (Thomson 2011).

Bronchial thermoplasty is an additional option for the management of patients with severe or refractory asthma. This newly approved procedure is both safe and effective and should be recommended accordingly.

### Oligonucleotides

The immune system branches into either innate or adaptive-mediated immunity that facilitates discrimination between self and nonself. The innate immune system is activated by early exposure to microbes, bacteria, and viruses

that use toll-like receptors (TLRs) (Fonseca 2009). The TLRs detect nonself and then activate both branches of the immune system. The TLRs bind to and are stimulated by unmethylated cytosine-phosphate-guanine dinucleotides in microbial DNA sequences (Gupta 2010); this leads to intracellular signaling (Sequin 2009) and the production of cytokines and chemokines (Parkinson 2008).

Similarly, CD4 T cells play a role in atopic conditions such as asthma. These cells can be separated into Th1 and Th2 cell types (see Figure 1-1). The hygiene hypothesis implicates Th2 in allergic diseases. Immunotherapy, or allergy shots, are believed to attack allergens by altering the immune response to Th2 and Th1. Activation of an antigen-presenting cell leads to secretion of chemokines and cytokines in the airway that in turn promote CD4 cell activation. That cell activation then augments CD4 cells' differentiation into Th1 cells. Oligonucleotides can replicate that reaction (Gupta 2010). Shifting the balance away from Th2-mediated response and toward the innate Th1 aspect can modify allergic or atopic diseases such as asthma. This has been shown in both animal and human trials. Administering both allergen and oligonucleotides to sensitized mice promoted Th1 responses and inhibited IgE production (Sequin 2009).

It was hypothesized that patients treated with unmethylated cytosine-phosphate-guanine dinucleotides would have a lessened allergic response. Patients with mild atopic asthma were given the inhaled oligonucleotide 1018 ISS followed by either an allergen inhalation challenge or placebo 24 hours later. Although 1018 ISS was demonstrated to be pharmacologically active, the 4-week treatment duration may have been insufficient to induce immunotherapy in human atopic disease (Gauvreau 2006). The oligonucleotide ASM8 reduces the allergen-induced early asthma response with a trend for a reducing late-asthmatic response. Trials have also evaluated oligonucleotides as adjuvants to immunotherapy; these hold promise because oligonucleotides are strong inducers of the Th1 response (Senti 2009).

Another emerging target for treatment of asthma specifically involves the TLRs because they are expressed on epithelial, smooth muscle, mast, and fibroblast cells. Activation of TLRs can induce a strong Th1 showing by modulating a response that commits T-helper cells to a Th1 over the Th2 phenotype (Meng 2011). That down-regulation of the Th2 response leads to fewer manifestations of allergic diseases and asthma (Fonseca 2009). Research has centered on TLR 3, TLR 7, and TLR 9, and specific agents are currently in phase I and II clinical trials (Table 1-5).

The lung is an ideal target for oligonucleotide and TLR therapy because of delivery by inhalation, prolonged duration of action in the lung, and little systemic toxicity. Still, these therapies face some challenges, including in vivo stability and the possibility of adverse effects such as immune stimulation, inflammation, and possible hypersensitivity or bronchoconstriction of the airway (Sequin 2009).

**Table 1-5.** Emerging Asthma Therapies in Clinical Development

Classification	Experimental Agents	Mechanism	Efficacy/Safety	Anticipated Benefit
Oligonucleotide agents	ASM8 1018 ISS AVE 0675 HYB 2093 CYT 003-QbG10 AIR 645	Promotes Th1 over Th2 response. Inhibits IgE production	Decreases allergen-induced early and late asthmatic response	Symptomatic patients already receiving immunotherapy
Toll-like receptor agents	GSK 2245035 AZD8818 AVE 0675 IMO-2134 SAR 21609	Modulates T-helper cells to a Th1 over the Th2 phenotype	Theoretical risk of overstimulating the immune system and inducing autoimmune diseases	Not yet known
CRTH2 antagonists	MK-7246 OC0000459 ARRY-005 ACT-129968 AMG 853	CRTH2 is a marker for Th2 cells	Improvement in FEV1, reduction in total IgE, and trend for reduction of sputum eosinophils	Not yet known
Monoclonal antibodies targeting IL-5	Mepolizumab Reslizumab Benralizumab (MEDI-563)	Reduces production, activation, and proliferation of eosinophils	Reduces exacerbation rates and eosinophil counts in both blood and sputum	Patients still symptomatic on conventional therapy and chronic oral corticosteroids
Monoclonal antibodies targeting IL-4	Alrakincept Pascolizumab (SB240683) Pitrakinra (Aerovant or AER 001) AMG 317	Blocking IL-4 decreases IgE production, mucus hypersecretion, airway hyperresponsiveness, and inflammatory cellular influx	Statistically significant changes in ACQ were not met; however, patients receiving highest-dose pitrakinra experienced fewer exacerbations vs. placebo	Symptomatic patients with atopic disease Patients with higher reversibility appear to have better responses Patients with high ACQ scores
Monoclonal antibodies targeting IL-9	MEDI-528	Theoretically, decreases mast cell infiltration of the lung, up-regulation of IL-13 and IL-5, eosinophil infiltration, AHR, and mucus production	Small, phase 2 study showed no effect on FeNO or the late asthmatic response	Not yet known
Monoclonal antibodies targeting IL-13	Tralokinumab (CAT-354) Anrukinzumab (IMA-638) QAX576 IMA-026 Lebrikizumab (MILR1444A)	Theoretically blocks AHR, eosinophilic inflammation, and mucus hypersecretion	Small, phase 1 study showed a T1/2 of 12 to 17 days and can be safely administered to patients with asthma	Not yet known

*(continued)*

**Table 1-5. Emerging Asthma Therapies in Clinical Development (continued)**

Classification	Experimental Agents	Mechanism	Efficacy/Safety	Anticipated Benefit
Drugs targeting TNF- $\alpha$	Infliximab Etanercept Golimumab (CNTO-148)	Reduction of TNF- $\alpha$ can lead to reduction in BHR and sputum neutrophils	Short-term efficacy seen in patients with severe disease. The dose of oral corticosteroids may be able to be reduced after initiation with a TNF- $\alpha$ agent. Safety concerns with golimumab include malignancies and pneumonia	Patients with FEV1 <60% predicted, 49 years or older, and those with onset of asthma at age 12 years or older

ACQ = Asthma Control Questionnaire; AHR = airway hyperresponsiveness; BHR = bronchial hyperresponsiveness; CRTH2 = chemoattractant receptor-homologous molecule; FeNO = fractional exhaled nitric oxide; IL = interleukin; Th = T-helper (cell); TNF- $\alpha$  = tumor necrosis factor- $\alpha$ . Information from Catley MC, Coote J, Bari M, Tomlinson KL. Monoclonal antibodies for the treatment of asthma. *Pharmacol Ther* 2011;132:333-51; Cho JY. Recent advances in mechanisms and treatments of airway remodeling in asthma: a message from the bench side to the clinic. *Korean J Intern Med* 2011;26:367-83; Corren J, Busse W, Meltzer EO, Mansfield L, et al. A randomized, controlled, phase 2 study of AMG317, an IL-4R $\alpha$  antagonist, in patients with asthma. *Am J Respir Crit Care Med* 2010;181:788-96; Dimov VV, Stokes JR, Casale TB. Immunomodulators in asthma therapy. *Curr All Asthma Rep* 2009;9:475-83; Desai D, Brightling C. Cytokine and anti-cytokine therapy in asthma: ready for the clinic? *Clin Exp Immunol* 2009;158:10-9; Ferrari N, Seguin R, Renzi P. Oligonucleotides: a multi-targeted approach for the treatment of respiratory diseases. *Future Med Chem* 2011;3:1647-62; Gauvreau GM, Boulet LP, Cockcroft DW, et al. Antisense therapy against CCR3 and the common beta chain attenuates allergen-induced eosinophilic responses. *Am J Respir Crit Care Med* 2008;177:952-8; Kanzler H, Barrat FJ, Hessel EM, et al. Therapeutic targeting of innate immunity with toll-like receptor agonists and antagonists. *Nature Medicine* 2007;13:552-9; Nguyen T-HT, Casale TB.

### Chemoattractant Receptor-Homologous Molecule

Researchers have identified chemoattractant receptor-homologous molecule (CRTH2) as a marker for human Th2 cells (Chevalier 2005). New evidence is mounting surrounding the role of prostaglandin D2, which is thought to elicit actions through the D-type prostanoid receptor. The prostaglandin binds to CRTH2 (Schuligoi 2010) and indomethacin. Scientists have used indomethacin, a CRTH2 agonist, as a starting block and have prepared novel CRTH2 DP2-selective antagonists (Birkinshaw 2006). Both CRTH2 and prostaglandin D2 are promising targets for antiasthma drug therapy (see Figure 1-1).

A novel CRTH2 antagonist, MK-7246, is reversible and highly selective for the human CRTH2 receptor (Gervais 2011). An oral CRTH2 antagonist (OC0000459) showed a 7.4% improvement in FEV1 at 28 days ( $p=0.037$ ). The OC0000459 agent also led to a reduction in total IgE concentration and a trend toward decreasing sputum eosinophils (Barnes 2012).

### Anticytokine Therapy

With the development of omalizumab, enthusiasm surrounding the identification and use of new biologics continues. Mast cells are important sources of cytokines, chemokines, proteases, prostaglandin D2, and histamine (Desai 2009). In the respiratory epithelium, dendritic cells network with the innate immune system, leading to

the release of cytokines; this initiates differentiation into either Th1 or Th2 cells. On one hand, interleukin-1, IL-6, and transforming growth factor- $\beta$  induce Th17, IL-12, and interferon-gamma (IFN- $\gamma$ )-promoting Th1 cell development. On the other hand, IL-4, IL-25, IL-33, and thymic stromal lymphopoietin drive Th2 differentiation (Desai 2009). Severe or refractory steroid-resistant asthma could be the result of a dominant Th1 phenotype using tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), IFN- $\gamma$ , IL-17, and IL-27. Using that theory, researchers have targeted single cytokines that are thought to play dominant roles (see Figure 1-1).

### Anti-IL-5

Two humanized anti-IL-5 therapies are undergoing premarket analysis. Mepolizumab, which is under investigation and in preclinical development by GlaxoSmithKline, reduces the production, activation, and proliferation of eosinophils (Smith 2011). Mepolizumab decreases exacerbation rates and the eosinophil counts in both blood and sputum (Halder 2009); it also allows for reductions in oral corticosteroid dosage without the risk of exacerbations (Parameswaran 2009). Mepolizumab reduces the number of asthma exacerbations experienced per year (Pavord 2012). This is an exciting advance for patients with uncontrolled severe asthma because it appears to be a safe and effective option that could lead to withdrawal of oral corticosteroids.

### **TNF- $\alpha$ Blockade**

Derived mainly from lymphocytes, mast cells, and macrophages, TNF- $\alpha$  leads to both increased bronchial hyperresponsiveness and sputum neutrophils and is an attractive target for severe asthma (Wenzel 2009). The use of anti-TNF- $\alpha$  agents has been shown to be effective in other inflammatory diseases such as rheumatoid arthritis and Crohn disease. Data with existing TNF- $\alpha$  agents such as etanercept for asthma show short-term efficacy for severe disease, but in patients with milder disease, its efficacy is modest (Antoniou 2009). Infliximab has limited data, suggesting that patients with moderate asthma uncontrolled by monotherapy with an ICS may experience fewer exacerbations (Erin 2006). A case series of 12 patients with concomitant rheumatoid arthritis and asthma who were taking etanercept (n=5), infliximab (n=3), or adalimumab (n=4) revealed that in those on oral corticosteroids, the dose could be reduced after initiation of the TNF- $\alpha$  inhibitor, and yet wheezing improved. Also, upon discontinuation of the TNF- $\alpha$  inhibitor, wheezing resumed (Stoll 2009).

A phase 2 study of golimumab in patients with severe persistent asthma was ended early at week 24 because of safety concerns that included increased incidence of malignancies (8 reported out of 231 patients) and infections such as pneumonia (Wenzel 2009). Subgroup analysis revealed a trend toward a lower risk of asthma exacerbations with golimumab versus placebo in the following subgroups: (1) patients 49 years or older, (2) patients with more than one ED visit or hospitalization in the year before the study, (3) patients with baseline prebronchodilator FEV1s less than 60% predicted, and (4) patients with asthma onset at 12 years of age or older (Wenzel 2009). Given the role of TNF- $\alpha$  in severe, refractory, or steroid-resistant asthma, future studies on the use of this anticytokine are needed to identify whether the long-term risk-benefit profile favors use in asthma.

### **Future Studies with Anticytokines**

Multiple preclinical trials are evaluating specific markers related to the asthma inflammatory cascade. The results of trials involving agents targeting IL-4, IL-13, IL-9, IL-12, IL-10, interferon- $\gamma$ , granulocyte-macrophage colony-stimulating factor, and even Th17 cells are anticipated (Hansbro 2011; Desai 2009). As understanding of the cytokine networks continues to evolve, so too will the potential targets for antiasthma therapy.

## **MONITORING**

Once patients are taking appropriate maintenance drugs, the emphasis turns to control. The patient's level of control should be assessed at each follow-up appointment (see Box 1-2). Patients who have well-controlled asthma can be seen every 6 months; patients whose asthma is less well controlled must be seen more routinely; and patients

whose asthma is poorly controlled should be assessed much more frequently (EPR-3, 2007). Print versions of the Asthma Control Test are available, as are [online interactive tools](#) that score and evaluate results for patients.

Overall, control of asthma is based on two components: (1) current signs or functional status; and (2) future risk of exacerbations. Typically, the worse the current signs, the higher the future risk. Patients often view control of their disease differently than their care providers. For example, survey data show that 32%–49% of patients experiencing severe asthma symptoms and 39%–70% of patients with moderate symptoms said their current level of asthma control was “well controlled” or “completely controlled” (Rabe 2004). Pharmacists are encouraged to educate patients not simply to accept symptoms and disruptions in their life but also to better understand what constitutes well-controlled asthma, and that controller adherence is a means to that end. Pharmacists should discuss Asthma Control Test results with patients and communicate such findings to providers.

Quality of life should be assessed periodically. Quality of life for children with asthma has been defined as the measure of emotions, asthma severity, symptoms, emergency department visits, missed school days, and activity limitations (Walker 2008). Pharmacists should ask patients, “Since your last visit, how many days did your asthma cause you to miss work or school, disturb your sleep, limit your activities, or cause an unscheduled visit to the ED or a hospital stay?” [Validated questionnaires](#) are available to gain an appreciation of how asthma affects quality of life.

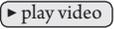
Clinical pharmacists should monitor for drug-related issues such as adherence or adverse events patients may be experiencing. Nonadherence with controller agents increases the risk of poor outcomes and additional health care costs. An analysis of e-prescription and filled-claims data revealed that 24% of first-time prescriptions were never picked up by patients (Fischer 2011). Factors associated with nonadherence included nonformulary status and cost of copayment.

Patients who fill first-time prescriptions in a lower copayment tier are more likely to refill them (Fischer 2011). Pharmacists should ensure prescriptions are covered on a patient's formulary at the lowest copayment tier. If available, controller drugs should be set up for automatic refill, thereby ensuring monthly fills and reminders. Pharmacists should assist uninsured patients to obtain drugs through manufacturers' patient assistance programs, local asthma coalitions, or channels developed by local chapters of national organizations such as the [Asthma and Allergy Foundation of America](#).

## **PATIENT EDUCATION**

Education for patients with asthma is multifaceted because it should cover the disease process; drugs, including proper inhalation and device technique; written

asthma action plans; and proper use of a peak flow meter. Coaching on how to manage acute symptoms and when to seek emergent care is also required. With their extensive knowledge of pathophysiology and therapeutics, pharmacists are suited to provide such educational services as part of the health care team.

Device technique instruction is imperative because improper use leads to poor outcomes. Regardless of the device selected, patients should be initially instructed on its use.  Adding a physical demonstration to both oral and written instructions is an effective way to improve device technique (Bosnic-Anticevich 2010). Routine review of proper technique is important: in one study, a decline in proper technique occurred with a time gap of just 2 months between teachings (Bosnic-Anticevich 2010). Also, repeated instruction over time improves regimen adherence (Takemura 2010). Patients should be instructed to bring all inhalers to appointments so that device technique can be assessed and documented frequently. Charting education topics and specifics regarding a patient's technique is helpful for the next follow-up. For patients with low literacy levels or who are nonnative speakers, technology aids may be appropriate. Videotaped instructions or computer-aided systems, as well as cartoons and pictographs, can be helpful (Kessels 2003).

Asthma self-management is often linked to education, behavioral modification, and trigger avoidance. Giving explicit instructions through a written asthma action plan provides patients with information to manage both chronic therapy and acute symptoms. Pharmacists should assess patients' baseline knowledge, determine whether any important cultural beliefs exist, and promote communication between patient and provider. If the beliefs and expectations of a health care provider differ from those of the patient—especially if the two have different cultural backgrounds or ethnicities—adherence can be impeded (Poureslami 2007). Open discussion about perspectives and beliefs facilitates communication between providers and patients and helps ensure that both perspectives are understood and negotiated (Poureslami 2007). By ensuring that patients understand the significance of adherence with their controller agents, treatment failure may be avoided.

Some patients have the common misconception that once their symptoms start to improve, the drug is no longer needed. Conversely, prescribers usually think every prescription written gets filled, picked up in a timely manner, used as directed, and refilled on time. Clinical pharmacists can educate both parties, including coaching patients on adherence and updating prescribers on actual patient drug use.

## QUALITY IMPROVEMENT

The Healthy People 2020 report targets several areas for improvement of asthma outcomes, including reducing asthma-related ED visits, hospitalizations, and deaths, as

well as increasing the proportion of patients receiving care according to the guidelines. The report pinpoints the need for written asthma management plans and formal patient education. Clinic- or community-based clinical pharmacists may help meet those targets by (1) monitoring the appropriateness of treatment plans, (2) educating patients on a written self-management plan, drugs, and device technique; and (3) providing formal education related to the patients' disease.

## PRACTICE MANAGEMENT

The role of clinical pharmacists in assisting or managing patients with asthma has been documented (Bunting 2006). In the community setting, pharmacists who integrate routine, brief asthma interventions into their daily work flow increase pharmacist-provider exchanges and successfully reach a large number of patients (Berry 2011). Taking advantage of frequent contact with patients during monthly refill encounters is an easy way to assess patients' asthma knowledge, discuss inhalation technique, and answer questions.

### Pharmacists as Certified Asthma Educators

To become a certified asthma educator (AE-C), a pharmacist must pass a national examination created and maintained by the National Asthma Educator Certification Board (NAECB). The mission of the NAECB is to “promote optimal asthma management and quality of life among individuals with asthma, their families, and communities by advancing excellence in asthma education through the certified asthma educator process.” Over 3000 asthma educators nationwide range from physicians, nurses, and respiratory therapists to community asthma educators; about 3% are pharmacists. In a survey of certificants, the majority of AE-Cs spend their time discussing asthma action plans; developing asthma programs; providing asthma education; offering, coordinating, or arranging asthma services; diagnosing or managing asthma; and performing and interpreting spirometry (Cataletto 2011). Pharmacists are excellent AE-C candidates because their education, training, and unique appreciation for drug, device, and patient education techniques are highly valued.

Professional development, added responsibilities, and job satisfaction are linked to becoming certified as a pharmacist (Cataletto 2011). Whether asthma education performed by pharmacists will be reimbursable in the future is unknown. However, the AE-C credential is recognized in many arenas of health care, and in some instances, is required for reimbursement by third-party payers.

Asthma education delivered by health professionals is important to the patient's overall care. For example, AE-Cs can help ensure patients understand disease pathology, the roles of controller and reliever drugs, the importance of adherence, how to monitor for acute changes in

symptoms, how to follow a written asthma action plan, and proper device technique. Further information on becoming an AE-C and on the self-assessment examination as well as the candidate handbook, containing a detailed content outline of the examination, are [available online](#).

### Role of Technology

An increasing proportion of patients are technologically savvy. By 2015, [a projected 65% of U.S. residents will have smartphones or tablet devices](#). The largest growth in smartphone ownership is among individuals 18 to 24 years old and those 45 to 54 years old (Gahran 2011). Free and low-cost smartphone applications are available to assist patients with asthma management. My Asthma Log enables patients to log asthma exacerbations and enter appointment dates. This application includes information on asthma drugs as well as links to videos on device technique. AsthmaSense includes a journaling feature, medication compliance reminders, and emergency contact information; it also offers users the ability to share data with caregivers. Plans are to improve this application with integrated sensors that will detect environmental changes in air quality and weather. Abriiz is marketed as a comprehensive asthma management system that lets a patient or caregiver create an online portal with information uploaded from a mobile device, as well as adherence features. Information is easily transmitted to a clinician for review. A loan-to-own program is available for eligible patients without access to a smartphone.

Other technological advances may improve compliance. The Asthmapolis sensor attaches to a rescue inhaler to collect data on when and where a patient experiences asthma symptoms. The sensor communicates with the patient's smartphone or base station and transmits the usage data, including location and time; this may include environmental triggers such as air quality or pollen levels. With the use of advanced technology and social media on the rise, pharmacists should be encouraged to become well versed in platforms that can help patients to better asthma management.

### CONCLUSION

As the prevalence of asthma rises, more health care resources will be consumed and may influence the morbidity associated with the disease. Pharmacists can help prevent acute exacerbations, ED visits, and hospitalizations by promoting controller drug adherence. Individuals with asthma require significant education related to the disease state, drug therapy, and device technique, which should be reinforced routinely. In the future, new targeted therapies may interfere with the underlying pathophysiology of asthma, its pharmacogenomics, or both, which may result in improved patient outcomes.

### REFERENCES

- Ali AK, Hartzema AG. Assessing the association between omalizumab and arteriothrombotic events through spontaneous adverse event reporting. *J Asthma All* 2012;5:1-9. [PubMed Link](#)
- Antoniou SA. Cytokine antagonists for the treatment of asthma. Progress to date. *Biodrugs* 2009;23:241-51. [PubMed Link](#)
- Barnes N, Pavord I, Chuchalin A, et al. A randomized, double-blind, placebo-controlled study of the CRTH2 antagonist OC000459 in moderate persistent asthma. *Clin Exp Allergy* 2012;42:38-48. [PubMed Link](#)
- Barnes PJ. Scientific rationale for using a single inhaler for asthma control. *Eur Respir J* 2007;29:587-95. [PubMed Link](#)
- Bateman ED, Kornmann O, Schmidt P, et al. Tiotropium is noninferior to salmeterol in maintaining improved lung function in  $\beta$ 16-ARG/ARG patients with asthma. *J Allergy Clin Immunol* 2011;128:315-22. [PubMed Link](#)
- Benavides S, Rodriguez JC, Maniscalco-Feichtl M. Pharmacist involvement in improving asthma outcomes in various healthcare settings: 1997 to present. *Ann Pharm* 2009; 43:85-97. [PubMed Link](#)
- Berry TM, Prosser TR, Wilson K, et al. Asthma friendly pharmacies: a model to improve communication and collaboration among pharmacists, patients, and healthcare providers. *J Urb Health* 2011;88(Supp 1):S113-25. [PubMed Link](#)
- Birkinshaw TN, Teague SJ, Beech C, et al. Discovery of potent CRTH2 (DP2) receptor antagonists. *Bioorg Med Chem Lett* 2006;16:4287-90. [PubMed Link](#)
- Blakey JD, Hall JP. Current progress in pharmacogenetics. *Br J Clin Pharmacol* 2011;71:824-31. [PubMed Link](#)
- Bosnic-Anticevich SZ, Sinha H, So S, et al. Metered-dose inhaler technique: the effect of two educational interventions delivered in community pharmacy over time. *J Asthma* 2010;47:251-6. [PubMed Link](#)
- Britto MT, Byczkowski TL, Hesse EA, et al. Overestimation of impairment-related asthma control by adolescents. *J Ped* 2011;158:1028-30. [PubMed Link](#)
- Brozek JL, Kraft M, Krishnan JA, et al. Long-acting  $\beta$ 2-agonist step-off in patients with controlled asthma. Systematic review with meta-analysis. *Arch Intern Med* 2012;172:1363-73. [PubMed Link](#)
- Bryant-Stephens T, Li Y. Outcomes of a home-based environmental remediation for urban children with asthma. *J N Med Assoc* 2008;100:306-16. [PubMed Link](#)

Bunting BA, Cranor CW. The Asheville Project: long term clinical, humanistic, and economic outcomes of a community-based medication therapy management program for asthma. *J Am Pharm Assoc* 2006; 46:133-47.

[PubMed Link](#)

Caillaud D, LeMerre C, Martinat Y, et al. A dose-ranging study of tiotropium delivered via Respimat SoftMist inhaler of handihaler in COPD patients. *Int J COPD* 2007;2:559-65.

[PubMed Link](#)

Carroll CL, Uygung B, Zucker AR, et al. Identifying an at-risk population of children with recurrent near-fatal asthma exacerbations. *J of Asthma* 2010;47:460-4.

[PubMed Link](#)

Castro M, Rubin AS, Laviolette M, et al. Effectiveness and safety of bronchial thermoplasty in the treatment of severe asthma; a multicenter, randomized, double-blind, sham-controlled clinical trial. *Am J Respir Crit Care Med* 2010;181:116-24.

[PubMed Link](#)

Cataletto M, Abramson S, Meyerson K, et al. The certified asthma educator: the United States experience. *Ped All Imm Pulm* 2011;24:159-63.

[Internet Link](#)

Chevalier E, Stock J, Fisher T, et al. Cutting edge: chemoattractant receptor-homologous molecule expressed on th2 cells plays a restricting role on IL-5 production and eosinophilic recruitment. *J Immunol* 2005;175:2056-60.

[PubMed Link](#)

Chowdhury BA, Dai Pan G. The FDA and safe use of long-acting beta-agonists in the treatment of asthma. *N Engl J Med* 2010;362:1169-71.

[PubMed Link](#)

Chung LP, Waterer G, Thompson PJ. Pharmacogenetics of  $\beta_2$  adrenergic receptor gene polymorphisms, long-acting  $\beta$ -agonists and asthma. *Clin Exp Allergy* 2011;41:312-26.

[PubMed Link](#)

Corvol H, Burchard EG. Pharmacogenetic response to albuterol among asthmatics. *Pharmacogenomics* 2008;9:505-10.

[PubMed Link](#)

Cox G, Laviolette M, Rubin A, et al. Long term safety of bronchial thermoplasty (BT): 3 year data from multiple studies. *Am J Respir Crit Care Med* 2009;179: A2780.

[Internet Link](#)

Cox G, Thomson NC, Rubin AS, et al. Asthma control during the year after bronchial thermoplasty. *N Engl J Med* 2007;356:1327-37.

[PubMed Link](#)

Cox LS. How safe are the biological in treating asthma and rhinitis? *All Asthma Clin Immunol* 2009;5(4). doi:10.1.1186/1710-1492-5-4.

[PubMed Link](#)

Desai D, Brightling C. Cytokine and anti-cytokine therapy in asthma: ready for the clinic? *Clin Exp Immunol* 2009;158:10-9.

[PubMed Link](#)

D'Urzo AD. Inhaled glucocorticosteroid and long-acting  $\beta_2$ -adrenoceptor agonist single-inhaler combination for both maintenance and rescue therapy. A paradigm shift in asthma management. *Treat Respir Med* 2006;5:385-91.

[PubMed Link](#)

Duhamel DR, Hales JB. Bronchial thermoplasty: a novel therapeutic approach to severe asthma. *J Vis Exp* 2010;4(45):pii2428.doi:10.3791/2428.

[PubMed Link](#)

Dweik RA, Boggs PB, Erzurum SC, et al. An official ATS clinical practice guideline: interpretation of exhaled nitric oxide levels (FENO) for clinical applications. *Am J Respir Crit Care Med* 2011;184:602-15.

[PubMed Link](#)

Erin EM, Leaker BR, Nicholson GC. The effects of a monoclonal antibody directed against tumor necrosis factor- $\alpha$  in asthma. *Am J Resp Crit Care Med* 2006;174:753-62.

[PubMed Link](#)

Expert Panel Report 3 (EPR3): guidelines for the diagnosis and management of asthma..

[Internet Link](#)

Fardon T, Haggart K, Lee DKC, et al. A proof of concept study to evaluate stepping down the dose of fluticasone in combination with salmeterol and tiotropium in severe persistent asthma. *Respir Med* 2007;101:1218-29.

[PubMed Link](#)

Fernandez C, Bevilacqua E, Fernandez N, et al. Asthma related to *Alternaria* sensitization: an analysis of skin-test and serum-specific IgE efficiency based on the bronchial provocation test. *Clin Exp Allergy* 2011; 41:649-56.

[PubMed Link](#)

Finkelstein Y, Bournissen FG, Hutson JR, et al. Polymorphism of the *ADRB2* gene and response to inhaled beta-agonists in children with asthma: a meta-analysis. *J Asthma* 2009; 46:900-5.

[PubMed Link](#)

Fischer MA, Choudhry NK, Brill G, et al. Trouble getting started; predictors of primary medication nonadherence. *Am J Med* 2011;124:1081.e9-1081.e22

[PubMed Link](#)

Flodin U, Jonsson P, Ziegler J, et al. An epidemiologic study of bronchial asthma and smoking. *Epidemiology* 1995;6:503-5.

[PubMed Link](#)

Fonseca DE, Kline JN. Use of CpG oligonucleotides in treatment of asthma and allergic disease. *Adv Drug Deliv Rev* 2009;61:256-62.

[PubMed Link](#)

Gabrio BJ. A new method to evaluate plume characteristics of hydrofluoroalkane and chlorofluorocarbon metered dose inhalers. *Int J Pharm* 1999;186:3-12.

[PubMed Link](#)

Gaffin JM, Phipatanakul W. The role of indoor allergens in the development of asthma. *Curr Opin Allergy Clin Immunol* 2009;9:128-35.

[PubMed Link](#)

Gao P. Sensitization to cockroach allergen: immune regulation and genetic determinants. *Clin and Dev Immunol* 2012.

[Internet Link](#)

Gauderman WJ, Avol E, Gilliland F, et al. The effect of air pollution on lung development from 10 to 18 years of age. *N Engl J Med* 2004;351:1057-67.

[PubMed Link](#)

Gauvreau GM, Hessel EM, Boulet LP, et al. Immunostimulatory sequences regulate interferon-inducible genes but not allergic airway responses. *Am J Respir Crit Care Med* 2006;174:15-20.

[PubMed Link](#)

Gentile DA, Skoner DP. New asthma drugs: small molecule inhaled corticosteroids. *Curr Opin Pharmacol* 2010;10:260-5.

[PubMed Link](#)

Gervais FG, Sawyer N, Stocco R, et al. Pharmacological characterization of MK-7246, a potent and selective CRTH2 (chemoattractant receptor-homologous molecule expressed on t-helper type 2 cells) antagonist. *Mol Pharmacol* 2011;79:69-76.

[PubMed Link](#)

Gildea TR, Khatri SB, Castro M. Bronchial thermoplasty: a new treatment for severe refractory asthma. *Cleveland Clinic J Med* 2011;78:477-85.

[PubMed Link](#)

Gosens R, Zaagsma J, Meurs H, et al. Muscarinic receptor signaling in the pathophysiology of asthma and COPD. *Respir Res* 2006;7:73-88.

[PubMed Link](#)

Gupta GK, Agrawal DK. CpG oligodeoxynucleotides as TLR9 agonists. *Biodrugs* 2010;24:225-35.

[PubMed Link](#)

Halder P, Brightling CE, Hargadon B, et al. Mepolizumab and exacerbations of refractory eosinophilic asthma. *N Engl J Med* 2009;360;10:973-84.

[PubMed Link](#)

Hall IP and Sayer I. Pharmacogenetics and asthma: false hope or new dawn? *Eur Respir J* 2007; 29:1239-45.

[PubMed Link](#)

Hansbro PM, Kaiko GE, Foster PS. Cytokine/anti-cytokine therapy-novel treatments for asthma? *BJ Pharmacol* 2011;163:81-95.

[PubMed Link](#)

Harver A, Schwartzstein RM, Kotses H, et al. Descriptors of breathlessness in children with persistent asthma. *Chest* 2011;139:832-8.

[PubMed Link](#)

Hendeles L, Colice GL, Meyer RJ. Withdrawal of albuterol inhalers containing chlorofluorocarbon propellants. *N Engl J Med* 2007;356:344-51.

[PubMed Link](#)

Hizawa N. Pharmacogenetics of  $\beta_2$ -agonists. *Allergology Int* 2011;60:239-46.

[PubMed Link](#)

Hizawa N. Beta-2 adrenergic receptor genetic polymorphisms and asthma. *J Clin Pharm Ther* 2009;34:631-43.

[PubMed Link](#)

Israel E, Chinchilli VM, Ford JG, et al. Use of regularly scheduled albuterol treatment in asthma: genotype-stratified, randomized, placebo-controlled cross-over trial. *Lancet* 2004;364:1505-12.

[PubMed Link](#)

Iwamoto H, Yokoyama A, Shiota N., et al. Tiotropium bromide is effective for severe asthma with noneosinophilic phenotype. *Eur Respir J* 2008;31:1379-82.

[PubMed Link](#)

Jick H, Hagberg KW, Egger P. Rate of suicide in patients taking montelukast. *Pharmacotherapy* 2009;29:165-6.

[PubMed Link](#)

Jindal SK, Gupta D. The relationship between tobacco smoke & bronchial asthma. *Indian J Med Res.* 2004;120:44353.

[PubMed Link](#)

Johnson JR, Hamid Q. Appraising the small airways in asthma. *Curr Opin Pulm Med* 2012;18:23-8.

[PubMed Link](#)

Kanazawa H. Anticholinergic agents in asthma: chronic bronchodilator therapy, relief of acute severe asthma, reduction of chronic viral inflammation and prevention of airway remodeling. *Curr Opin Pulm Med* 2008;12:60-67.

[PubMed Link](#)

Keogh B, Parker AE. Toll-like receptors as targets for immune disorders. *Trends Pharmacol Sci* 2011;32:435-42.

[PubMed Link](#)

Kerstjens HA, Disse B, Schroder-Babo W, et al. Tiotropium improves lung function in patients with severe uncontrolled asthma: a randomized controlled trial. *J All Clin Immunol* 2011 128:308-14.

[PubMed Link](#)

Kerstjens HA, Engel M, Dahl R, et al. Tiotropium in asthma poorly controlled with standard combination therapy. *NEJM* 2012;367:1198-1207.

[PubMed Link](#)

Kessels RPC. Patients' memory for medical information. *J R S Med* 2003;96:219-22.

[PubMed Link](#)

Kim SH, Ye YM, Hur GY, et al. Effect of  $\beta_2$ -adrenergic receptor polymorphism in asthma control of patients receiving combination treatment. *Yonsei Med J* 2009;50:182-8.

[PubMed Link](#)

Komarow HD, Myles IA, Uzzaman A, et al. Impulse oscillometry in the evaluation of diseases of the airways in children. *Ann Allergy Asthma Immunol* 2011;106:191-99.

[PubMed Link](#)

Kramer JM. Balancing the benefits and risks of inhaled long-acting beta-agonists – the influence of values. *N Engl J Med* 2009;360:1592-5.

[PubMed Link](#)

Kuna P, Peters MJ, Manjra AI, et al. Effect of budesonide/formoterol maintenance and reliever therapy on asthma exacerbations. *Int J Clin Pract* 2007;61:725-36.

[PubMed Link](#)

Lang JE. Obesity, nutrition, and asthma in children. *Ped All, Immunol, and Pulm.* 2012 25:64-75.

[PubMed Link](#)

Lemanske RF, Mauger DT, Sorkness CA, et al. Step-up therapy for children with uncontrolled asthma receiving inhaled corticosteroids. *NEJM* 2010;362:975-85.

[PubMed Link](#)

Lima JJ, Blake KV, Tantisira KG, et al. Pharmacogenetics of asthma. *Curr Opin Pulm Med* 2009; 15:57-62.

[PubMed Link](#)

Lima JJ, Thomason DB, Mohamed MHN, et al. Impact of genetic polymorphisms of the  $\beta_2$ -adrenergic receptor on albuterol bronchodilator pharmacodynamics. *Clin Pharm Ther* 1999; 65: 519-25.

[PubMed Link](#)

Lodge CJ, Allen KJ, Lowe AJ, et al. Perinatal cat and dog exposure and the risk of asthma and allergy in the urban environment: a systematic review of longitudinal studies. *Clin and Dev Immunol* 2012.

[PubMed Link](#)

Louis R, Joos G, Michilis A, et al. A comparison of budesonide/formoterol maintenance and reliever therapy vs. conventional best practice in asthma management. *Int J Clin Pract* 2009;63:1479-88.

[PubMed Link](#)

Lugogo L, Kraft M, Dixon AE. Does obesity produce a distinct asthma phenotype? *J Appl Physiol* 2010; 108:729-34.

[PubMed Link](#)

McCabe JC, Koppenhagen F, Blair J, et al. ProAir HFA delivers warmer, lower-impact, longer-duration plumes containing higher fine particle dose than Ventolin HFA. *J Aero Med Pulm Drug Del* 2012; 25:104-9.

[PubMed Link](#)

McCormack PL, Lyseng-Williamson KA. Budesonide/formoterol A review of its use as maintenance and reliever inhalation therapy in asthma. *Drugs* 2007;67:2407-31.

[PubMed Link](#)

McGavin JK, Goa KL, Jarvis B. Inhaled budesonide/formoterol combination. *Drugs* 2001;61:71-8.

[PubMed Link](#)

Meng L, He X, Zhu W, et al. TLR3 and TLR7 modulate IgE production in antigen induced pulmonary inflammation via influencing IL-4 expression in immune organs. *PLoS One* 2011. 6(2):e17252.doi:10.1371/journal.pone.0017252.

[PubMed Link](#)

Mepolizumab. *Drugs R D.* 2008;9:125-30.

[PubMed Link](#)

Metzger NL, Kochler DR, Gravatt LAH. Confirmed B16 ARG/ARG polymorphism in a patient with uncontrolled asthma. *Ann Pharm* 2008;42:874-81.

[PubMed Link](#)

Munakata M. Exhaled nitric oxide (FeNO) as a non-invasive marker of airway inflammation. *Allergo Inter* 2012.

[PubMed Link](#)

Nelson HS, Weiss ST, Bleecker ER, et al. The salmeterol multicenter asthma research trial: a comparison of usual pharmacotherapy for asthma or usual pharmacotherapy plus salmeterol. *Chest* 2006;129:15-26.

[PubMed Link](#)

O'Byrne PM, Bisgaard H, Godard PP, et al. Budesonide/formoterol combination therapy as both maintenance and reliever medication in asthma. *Am J Respir Crit Care Med* 2005; 171:129-36.

[PubMed Link](#)

O'Connor BJ, Towse LJ, Barnes PJ. Prolonged effect of tiotropium bromide on methacholine-induced bronchoconstriction in asthma. *J Respir Crit Care Med* 1996(154):876-80.

[PubMed Link](#)

Ogden CL, Carroll MD, Kit BK, et al. Prevalence of obesity in the United States, 2009-2010.

[Internet Link](#)

Okada H, Kuhn C, Feillet H, et al. The "hygiene hypothesis" for autoimmune and allergic diseases: an update. *Clin & Exp Immunol* 2010;160:1-9.

[PubMed Link](#)

U.S. Department of Health and Human Services. Orange Book: Approved drug products with therapeutic equivalence evaluations.

[Internet Link](#)

Park HW, Yang MS, Park CS, et al. Additive role of tiotropium in severe asthmatics and Arg16Gly in ADRB2 as a potential marker to predict response. *Allergy* 2009;64:778-83.

[PubMed Link](#)

Parkinson T. The future of toll-like receptor therapeutics. *Curr Opin Molec Therap* 2008;10:21-31.

[PubMed Link](#)

Parameswaran N, Pizzichin MMM, Kjarsgaard M, et al. Mepolizumab for prednisone-dependent asthma with sputum eosinophilia. *N Engl J Med* 2009;360:985-93.

[PubMed Link](#)

Pauwels RA, Sears MR, Campbell M, et al. Formoterol as relief medication in asthma: a worldwide safety and effectiveness trial. *Eur Respir J* 2003;22:787-94.

[PubMed Link](#)

Pavord ID, Cox G, Thomson NC. The RISA trial study group, et al. Safety and Efficacy of bronchial thermoplasty in symptomatic, severe asthma. *Am J Respir Crit Care Med* 2007; 176: 1185-91.

[PubMed Link](#)

Pavord, ID, Korn S, Howarth P, et al. Mepolizumab for severe eosinophilic asthma (DREAM): a multicenter, double-blind, placebo-controlled trial. *Lancet* 2012;380:651-9.

[PubMed Link](#)

- Peters SP, Kunselman SJ, Icitovic N, et al. Tiotropium bromide step up therapy for adults with uncontrolled asthma. *N Engl J Med* 2010;363:1715-26.  
[PubMed Link](#)
- Petsky HL, Cates CJ, Li A, et al. Tailored interventions based on exhaled nitric oxide versus clinical symptoms for asthma in children and adults. *Cochrane Database of Systemic Reviews* 2009, issue 4. Art No.: CD006340. DOI: 10.1002/14651858.CD006340.pub3  
[PubMed Link](#)
- Poureslami IM, Rootman I, Balka E, et al. A Systematic Review of Asthma and Health Literacy: A Cultural-Ethnic Perspective in Canada. *Med Gen Med* 2007;9:40.  
[PubMed Link](#)
- Rabe KF, Atienza T, Magyar P. Effect of budesonide in combination with formoterol for reliever therapy in asthma exacerbation: a randomized controlled, double-blind study. *Lancet* 2006a; 368:744-53.  
[PubMed Link](#)
- Rabe KF, Pizzichini E, Stallberg B, et al. Budesonide/formoterol in a single inhaler for maintenance and relief in mild-to-moderate asthma. A randomized, double-blind trial. *CHEST* 2006b;129:246-56.  
[PubMed Link](#)
- Rabe KF, Adachi M, Lai C, et al. Worldwide severity and control of asthma in children and adults: The global asthma insights and reality surveys. *J Allergy Clin Immunol* 2004;114:40-7.  
[PubMed Link](#)
- Rank MA, Wollan P, Li JT, et al. Trigger recognition and management in poorly controlled asthmatics. *Allergy Asthma Proc* 2010; 31:e99-105.  
[PubMed Link](#)
- Rosenlund M, Forastiere F, Porta D, et al. Traffic-related air pollution in relation to respiratory symptoms, allergic sensitization, and lung function in schoolchildren. *Thorax* 2009;64:573-80.  
[PubMed Link](#)
- Schatz M. Improving asthma outcomes in large populations. *J Allergy Clin Immunol* 2011;128:273-7.  
[PubMed Link](#)
- Schroder NWJ, Crother TR, Naiki Y, et al. Innate immune responses during respiratory infection with a bacterial pathogen induce allergic airway sensitization. *J Allergy Clin Immunol* 2008;122:595-602.  
[PubMed Link](#)
- Schuligoj R, Strum E, Luschnig P, et al. CRTH2 and D-type prostanoid receptor antagonists as novel therapeutic agents for inflammatory diseases. *Pharmacology* 2010;85:372-82.  
[PubMed Link](#)
- Schumock GT, Lee TA, Joo MJ, et al. Association between leukotriene-modifying agents and suicide. What is the evidence? *Drug Saf* 2011;34:533-44.  
[PubMed Link](#)
- Schumock GT, Stayner LT, Valuck RJ, et al. Risk of suicide attempt in asthmatic children and young adults prescribed leukotriene-modifying agents: a nested case-control study. *J Allergy Clin Immunol* 2012;130:368-75.  
[PubMed Link](#)
- Senti G, Johansen P, Haug S, et al. Use of A-type CpG oligodeoxynucleotides as an adjuvant in allergen-specific immunotherapy in humans: a phase I/IIa clinical trial. *Clin Exp Allergy*, 2009;29:562-70.  
[PubMed Link](#)
- Smith DA, Minthorn EA, Beerah M. Pharmacokinetics and pharmacodynamics of mepolizumab, an anti-interleukin-5 monoclonal antibody. *Clin Pharmacokinet* 2011;50:215-27.  
[PubMed Link](#)
- Smith HJ, Reinhold P, Goldman MD. Chapter 5. Forced oscillation technique and impulse oscillometry. In: *Eur Respir Mon.* United Kingdom, 2005;31:72-105.  
[Internet Link](#)
- Song TW, Kim KW, Kim ES, et al. Correlation between spirometry and impulse oscillometry in children with asthma. *Acta Paediatrica* 2008;91:51-4.  
[PubMed Link](#)
- Spitzer WO, Suissa SM, Ernst P, et al. The use of  $\beta$ -agonists and the risk of death and near death from asthma. *N Engl J Med* 1992; 326:501-6.  
[PubMed Link](#)
- Stocks J, DeZateux C. The effect of parental smoking on lung function and development during infancy. *Respirology* 2003;8:266-85.  
[PubMed Link](#)
- Stoll ML, Solomon DH, Batra KL, et al. TNF inhibitors may improve asthma symptoms: a case series of 12 patients with rheumatoid arthritis and asthma. *J Clin Rheumatol* 2009;15:198-200.  
[PubMed Link](#)
- Sverrild A, Porsbjerg C, Thomsen SF, et al. Airway hyperresponsiveness to mannitol and methacholine and exhaled nitric oxide: a random-sample population study. *J Allergy Clin Immunol* 2010;952-8.  
[PubMed Link](#)
- Takemura M, Kobayashi M, Kimura K, et al. Repeated instruction on inhalation technique improves adherence to the therapeutic regimen in asthma. *J Asthma* 2010;47:202-8.  
[PubMed Link](#)
- Takizawa H. Impact of air pollution on allergic diseases. *Korean J Intern Med* 2011;26:262-73.  
[PubMed Link](#)
- Tanaka H, Hozawa S, Kitada J, et al. Impulse oscillometry; therapeutic impacts of transdermal long-acting beta-2 agonist patch in elderly asthma with inhaled corticosteroid alone. *Allergol Int.* 2012. <http://ai.jsaweb.jp/pdf/12-RAI-0461.pdf> Accessed July 11, 2012.  
[PubMed Link](#)
- Thomson NC, Rubin AS, Niven RM, et al. Long-term (5 year) safety of bronchial thermoplasty: Asthma intervention research (AIR) trial. *BMC Pulmonary Medicine* 2011; 11(8).  
[PubMed Link](#)

Tse SM, Tantisira K, Weiss ST. The pharmacogenetics and pharmacogenomics of asthma therapy. *Pharmacogenomics J* 2011;11:383-92.

[PubMed Link](#)

van den Berge, M. ten Hacken NHT, Cohen J, et al. Small airway disease in asthma and COPD. *Chest* 2011;139:412-23.

[PubMed Link](#)

Vaessen-Verberne AAPH, van den Berg NJ, van Nierop JC, et al. Combination therapy salmeterol/fluticasone versus doubling dose of fluticasone in children with asthma. *Am J Resp Crit Care Med* 2010;182:1221-7.

[PubMed Link](#)

Wahidi MM, Kraft M. Bronchial thermoplasty for severe asthma. *Am J Respir Crit Care Med* 2012. 185:709-14.

[PubMed Link](#)

Walker J, Winkelstein M, Land C, et al. Factors that influence quality of life in rural children with asthma and their parents. *J Pediatr Health Care* 2008;22:343-50.

[PubMed Link](#)

Wechsler ME, Kunselman SJ, Chinchilli VM, et al. Effect of  $\beta_2$ -adrenergic receptor polymorphism on response to longacting  $\beta_2$  agonist in asthma (LARGE trial): a genotype-stratified, randomized, placebo-controlled, crossover trial. *Lancet* 2009;274:1754-64.

[PubMed Link](#)

Wenzel S, Barnes PJ, Bleeker ER, et al. A randomized, double-blind, placebo-controlled study of tumor necrosis factor- $\alpha$  blockage in severe persistent asthma. *Am J Resp Crit Care Med* 2009;179:549-58.

[PubMed Link](#)

Yates DH. Role of exhaled nitric oxide in asthma. *Imm Cell Biol* 2001;79:178-90.

[PubMed Link](#)

# SELF-ASSESSMENT QUESTIONS

1. A 32-year-old woman (height 5'4", weight 189 lb) with persistent asthma complains of shortness of breath (SOB) and wheezing twice weekly. She uses her albuterol hydrofluoroalkane (HFA) inhaler two times a week, usually when outside at the park. She wakes up at night coughing about once weekly. Her current drugs include albuterol HFA 1-2 puffs every 4–6 hours as needed for SOB, fluticasone/salmeterol diskus 250/50 one puff twice daily, loratadine 10 mg once daily for “allergies”, fluticasone nasal spray 50 mcg 2 sprays each nostril once daily, and metformin 500 mg twice daily. Sertraline 50 mg once daily was initiated 2 months ago. She does not have a peak flow meter but follows her asthma action plan. The patient cannot remember the last time she had to visit the emergency department (ED) for an exacerbation. Her medical history includes allergic rhinitis, depression, and polycystic ovary syndrome. Her BP is 110/76 mm Hg. Which one of the following would best address this patient’s current symptoms?

- A. Add montelukast 10 mg once daily at bedtime.
- B. Discontinue fluticasone/salmeterol combination. Initiate fluticasone 250 mcg diskus 1 puff twice daily
- C. Discontinue fluticasone/salmeterol combination. Initiate fluticasone 250 mcg diskus 2 puffs twice daily.
- D. Add theophylline 200-mg sustained-release tablet once daily.

2. A 30-month old boy with asthma presents for a follow-up appointment accompanied by his mother, father, and paternal grandmother. The boy has visited the ED five times in the past year for exacerbations and was admitted to the pediatric intensive care unit twice in the past year for asthma treatment. His family history includes asthma (mother, maternal grandfather), hypertension (paternal grandfather), and allergic rhinitis (father). The patient’s mother smokes but not in the house or car. His laboratory tests show blood eosinophilia: 3%, sputum: predominant eosinophils. The patient’s father is a high school basketball coach and is very concerned about his son’s ability to play sports in school. The family asks you what the chances are that the boy will continue to have asthma as a teenager and adult. Which one of the following is the best response to this family’s query?

- A. All children with asthma will have symptoms into adulthood.
- B. His chances are quite good because of the eosinophils found in his blood and sputum.

- C. His chances are quite good because of past exacerbation history and Mom with asthma.
- D. The chance of continued asthma is low and he should grow out of his asthma by age 10.

## Questions 3 and 4 pertain to the following case.

Y.P. is a 26-year-old man who comes in to pick up a refill on his Ventolin HFA inhaler. He is asked to demonstrate his inhalation and device technique. [▶ play video](#)

3. Which of the following is the most appropriate feedback on Y.P.’s inhalation technique?

- A. Breath holding for 5 seconds and exhalation for 5 seconds after your dose was appropriate for drug deposition.
- B. The mouthpiece doesn’t need to be inspected if lid was sealed and the canister does not need to be shaken.
- C. Your slow inhalation rate and total time spent inhaling of 2 seconds was adequate
- D. The pause during inhalation and resumption with one more second of inhalation may result in less drug reaching your lungs.

4. Which one of the following is best for Y.P. at this time?

- A. Change to ProAir HFA as rescue medication.
- B. Educate further on appropriate inhalation technique.
- C. Change to Xopenex HFA for rescue medication.
- D. Educate on the use of albuterol nebulized solution instead.

5. A 35-year-old African American man has very poorly controlled persistent asthma. His current drugs include mometasone 200 mcg twisthaler 1 puff twice daily, formoterol aerolizer 12 mcg capsule inhaled twice daily, prednisone 5 mg once daily, albuterol HFA 1-2 puffs every 4–6 hours as needed for SOB, and omeprazole 20 mg once daily. The patient uses a phone alarm to remind him when to take his drugs and inhalations on time. Refill histories show he is adherent. He wants his breathing to be better controlled and says he has been doing research online. He asks if he should get his “genes tested.” Which one of the following is the best response to this patient?

- A. No. Genetic testing is not recommended in patients that are on an appropriate treatment regimen.
- B. No. African Americans are advised against genetic testing because they do not have genetic polymorphisms implicated in asthma.

- C. Yes. If identified, genetic markers may help us distinguish why your medications are inadequate.
- D. Yes. Genetic testing may be useful to help us determine if you can discontinue your prednisone.

**Questions 6–8 pertain to the following case.**

Q.T. is a 32-year-old woman with asthma. Her current drugs include a medium-dose inhaled corticosteroid (ICS) plus a long-acting  $\beta$ -agonist (LABA), a short-acting  $\beta$ -agonist (SABA) for rescue use, montelukast 10 mg once daily, fexofenadine 180 mg once daily, and a prenatal vitamin once daily. Q.T. still experiences daily wheezing, but she is still able to make it to the gym most days. She states she wakes up with a “tight chest” and coughing about twice per week and uses her rescue medicine at least 3 days per week. She checks her peak flow occasionally; she states it is typically in her yellow zone based on a personal best she recorded 2 years ago. She recently got married and is interested in family planning. She is concerned about her asthma control if she becomes pregnant and has investigated genetic testing. Q.T. seeks your advice regarding how to interpret the results of her “at-home DNA” sample which reveal she is positive for the 16Arg/Arg polymorphism.

6. Which one of the following is the best education point to give Q.T.?
  - A. Your rescue medication is appropriate given your phenotype.
  - B. The effectiveness of your LABA may be less than desirable
  - C. Montelukast may not provide added benefit for your asthma.
  - D. LABAs are contraindicated for 16Arg/Arg patients.
7. Based on both her genetic findings and current symptoms, which of the following is the most appropriate change to Q.T.’s current regimen?
  - A. Discontinue montelukast.
  - B. Add omalizumab.
  - C. High-dose ICS plus LABA.
  - D. Add prednisone daily.
8. Two months after starting her new regimen, Q.T. is still experiencing symptoms and her asthma is assessed as not well controlled. Which one of the following is best to recommend for Q.T.?
  - A. Bronchial thermoplasty.
  - B. Sputum induction test.
  - C. Fraction of exhaled nitric oxide (FeNO) assessment.

- D. Prednisone 2.5 mg daily

**Questions 9–12 pertain to the following case.**

S.B. is a 43-year-old African American woman (height 5’4”, weight 143 lb) with severe persistent asthma, rheumatoid arthritis in her hands, allergic rhinitis, eczema, gastroesophageal reflux disease, and type 2 diabetes mellitus. Her current drugs are ciclesonide 160 mcg/puff 2 puffs twice daily, albuterol HFA 1 or 2 puffs every 4–6 hours as needed for wheezing/SOB, zafirlukast 20 mg twice daily, methotrexate 20 mg weekly, folic acid 1 mg daily, fluticasone 50 mcg/spray 2 sprays each nostril once daily, mometasone cream 0.1% twice daily to affected skin, metformin 1g twice daily, glipizide XL 10 mg once daily, and aspirin 81 mg once daily. Examination shows her oxygen saturation at 90% on room air; her blood pressure is 134/84 mm Hg, and her heart rate is 94 beats/minute. Her father died at age 74 after a myocardial infarction (MI), and her mother has type 2 diabetes mellitus and rheumatoid arthritis. S.B. checks her peak flow rates routinely and they typically are between 270–280 L/minute in the morning. Her personal best is 350 L/minute. Laboratory results are as follows: IgE level 524 U/mL (normal: 4.2–595 U/mL); skin prick testing (+) feather mix, cat hair, dog hair, rat epithelial (+) Bermuda grass, hickory/pecan mix (+) Dermatophagoides farinae (dust mites). S.B. hands you a prescription for salmeterol Diskus. “I want to breathe better so I can keep up with my kids, but I’ve heard this medicine is deadly. Should I be worried?”

9. Which one of the following is the best response to give S.B.?
  - A. Salmeterol is better avoided by African Americans, so let me call your doctor to recommend an alternative.
  - B. New evidence shows salmeterol can cause problems, but this is likely OK because you are taking another controller medicine.
  - C. New evidence shows salmeterol can cause problems, but this is likely OK for you because your asthma is controlled.
  - D. Salmeterol is fine for your asthma, but let me recommend to your doctor a device that will be easier for you to use.
10. S.B. returns 2 months later and reports some improvement in her asthma control. She states she is still experiences a “runny nose and itchy, watery eyes” nightly and has to always keep tissues on hand. She is using her albuterol less (down to once per week) and her asthma control test score is 19. Which one of the following would provide the most benefit to S.B.?
  - A. Omalizumab.
  - B. Prednisone.

- C. Montelukast.  
D. Famotidine.
11. On the basis of her current signs and symptoms, which one of the following emerging therapies for asthma would have the most theoretical benefit for S.B.?
- A. Oligonucleotide.  
B. Anti-TNF- $\alpha$ .  
C. A chemoattractant receptor-homologous molecule (CRTH2) antagonist.  
D. A DP-receptor agonist.
12. Which one of the following nonpharmacologic techniques is best to recommend for S.B.?
- A. Acupuncture treatments.  
B. Mattress and pillow encasings.  
C. A basement dehumidifier.  
D. Elevate the head of her bed.
13. A 40-year-old man with asthma (height 5'9", weight 283 lb) routinely participates as a research subject in ongoing asthma trials. He states "I'm always looking for the next best thing to make my asthma better. I just want to sleep better and not have symptoms at work that require me to take breaks and use my rescue inhaler. I'd also like to cut down on visits to the ED. I'm worried my boss is going to kick me off his insurance because I've had so many hospital stays!" The patient's medical history includes poorly controlled asthma, eczema, migraine headaches, and obesity. His current drugs are salmeterol/fluticasone 250/50 mcg 1 puff twice daily, prednisone 5 mg once daily, sumatriptan 100 mg as needed for headaches, and orlistat 60 mg twice daily. His vital signs are: blood pressure 138/78 mm Hg, heart rate 74 beats/minute, temperature 97.9°F, IgE concentration 100 U/mL (normal 4.2–595 U/mL). His sputum induction test shows (+) eosinophils (5%). Blood eosinophils are (+): 600 cells/mL (normal < 350 cells/mL). Which one of the following emerging therapies would be best to recommend for this patient?
- A. A CRTH2 antagonist.  
B. Oligonucleotide.  
C. Anti-IL-5.  
D. A TNF- $\alpha$  antagonist.
14. Four patients all have very poorly controlled asthma on high dose ICS plus LABA. Which one of these patients would theoretically benefit the most from a trial of CNTO-148 (golimumab)?
- A. A 50-year-old architect with severe plaque psoriasis.  
B. An 18-year-old college freshman with irritable bowel disease.  
C. A 62-year-old retired man with osteoarthritis of the knee.  
D. A 24-year-old man with poorly controlled bipolar disorder.
15. A 13-year-old girl is accompanied by her mother for a follow-up asthma appointment. The patient is difficult to communicate with as she rarely looks up from her iPhone and is texting throughout the visit. Her mother states the girl uses her iPhone regularly, has an iPad at home, and uses the family desktop computer for homework. She adds that her daughter is quite mature for her age and doesn't like to be treated like a small child. The mother states she lays her medicine out for her daughter every morning and evening but they are rarely "empty" when she gets her monthly refill. The patient has had allergen skin prick testing and knows her asthma triggers are dust, tobacco smoke, and animal dander. The mother also states that the girl has given up on the idea of trying out for the school volleyball team this year because of her problems with breathing. The patient's medical history includes poorly controlled asthma, allergic rhinitis, and attention deficit/hyperactivity disorder. A chart review reveals the patient routinely shows up for appointments, and her refill history shows monthly fills. The girl demonstrates adequate device technique with her metered-dose inhaler. Her current drugs are budesonide/formoterol metered-dose inhaler 160/4.5 mcg 1 puff twice daily, desloratadine 10 mg once daily, methylphenidate 10 mg three times daily, and albuterol HFA 1 or 2 puffs every 4-6 hours as needed for wheezing or SOB. Which one of the following technological aids would be best to recommend for this patient?
- A. AsthmaSense.  
B. abriIz.  
C. Asthmapolis.  
D. My Asthma Log.
16. A 39-year-old man (height 6'1", weight 200 lb) is seen for a follow-up asthma appointment. His medical history includes very poorly controlled asthma, erectile dysfunction, degenerative disk disease, and hypertension. His current drugs include mometasone/formoterol 200/5 mcg 2 puff twice daily, albuterol HFA 1 or 2 puffs every 4–6 hours as needed for shortness of breath/wheezing, sildenafil 50 mg as needed, naproxen 500 mg twice daily, hydrochlorothiazide 12.5 mg once daily, and calcium/vitamin D (500/500 mg) 1 tablet twice daily with meals. His vital signs are oxygen saturation 97% on room air, blood pressure 130/74 mm Hg, heart rate 90 beats/minute, peak

expiratory flow 300 L/minute (best of three with adequate effort, personal best 550 L/minute). His social history is positive for tobacco use (one-half pack per day), and he states that he doesn't drink alcohol or take illicit drugs. An induced sputum sample predominant WBC found: neutrophils. Other test results are: FeNO 8 parts/billion and IgE 250 U/L (normal range, 4–595 U/L). Skin prick testing: (-) grasses, trees, and animal allergens. Four months ago, his pulmonary function test results were as follows:

Test	Pre-bronchodilator	Post-bronchodilator
FEV <sub>1</sub>	72	80
FEV <sub>1</sub> /FVC	59	82
FVC	73	79

Which one of the following would be best to add to his regimen?

- A. Tiotropium Handihaler 18 mcg once daily.
  - B. Montelukast 10 mg once daily at bedtime.
  - C. Mometasone/formoterol 200/5 mcg 4 puffs twice daily.
  - D. Omalizumab 300 mg subcutaneously injected every 2 weeks.
17. A 45-year-old African American woman (height 5'7", weight 180 lb) has a medical history that includes persistent asthma, allergic rhinitis, polycystic ovary syndrome, and type 2 diabetes mellitus. Her current drugs are fluticasone HFA 220 1 puff twice daily, prednisone 5 mg once daily, metformin 500 mg twice daily, and albuterol HFA 1 or 2 puffs every 4–6 hours as needed for shortness of breath. She uses her rescue inhaler several times per day, wakes up coughing and wheezing 5–6 times per week, and can no longer participate in her weekly yoga class. The patient's Asthma Control Test score is 10. Her vital signs include blood pressure 100/82 mm Hg and heart rate 80 beats/minute. Her genotype is 27Glu/Glu. A sputum test shows predominant eosinophils. Other test results are FeNO 4 parts/billion and IgE 100 U/L. Skin prick testing results are: (-) ragweed, pigweed, (-) ladybug, cat hair, feather mix, (-) *Alternaria alternata*.

Which one of the following is most appropriate to recommend for this patient?

- A. Continue current drug regimen.
  - B. Add tiotropium 18 mcg once daily.
  - C. Increase prednisone to 10 mg by mouth once daily.
  - D. Fluticasone/salmeterol HFA 230/21 2 puffs twice daily.
18. A 36-year-old woman (height 5'4", weight 102 lb) has a medical history that includes persistent asthma,

allergic rhinitis, and osteopenia. Her current drugs are fluticasone/salmeterol diskus 500/50 mcg 1 puff twice daily, prednisone 2.5 mg once daily, albuterol HFA 1 or 2 puffs every 4–6 hours as needed for shortness of breath, levocetirizine 5 mg once daily, alendronate 35 mg once weekly, calcium/vitamin D twice daily, and omalizumab injections once monthly. She was started on tiotropium 18 mcg once daily 3 months ago, and pharmacy claims data reveal she is adherent to all medications. She uses her rescue inhaler several times per day, wakes up wheezing 4 or 5 times per week, and is no longer able to participate in her select volleyball team because of symptoms. Her Asthma Control Test score is 8. Her vital signs are blood pressure 110/62 mm Hg and heart rate 70 beats/minute. Her genotype is Arg16/Gly. A sputum sample shows predominant eosinophils. Other test results are FeNO 54 parts/billion, IgE 50 u/L, and skin prick testing (+) ragweed, pigweed, cat hair, feather mix, (+) *Alternaria alternata*. Which of the following is best to recommend for this patient?

- A. Increase omalizumab to twice monthly injections and prednisone to 5 mg daily.
  - B. Discontinue tiotropium and add montelukast 10 mg once daily.
  - C. Continue tiotropium and schedule her for bronchial thermoplasty.
  - D. Switch albuterol to ipratropium as her rescue medication and discontinue prednisone.
19. A 52-year-old man (height 5'9", weight 190 lb) is following up on his asthma drug regimen. He was told to make the appointment because of his "out of control" asthma. He states he isn't able to attend bowling league, often uses his rescue medicine both at home and at work, and is having frequent nighttime symptoms and awakenings. The patient works as a technician for a spray-on truck bed liner company. His medical history includes asthma and carpal tunnel syndrome.

His medications and refill record are summarized in the table below.

Drug	Fill dates	Refills remaining	Notes
Fluticasone/salmeterol 500/50 1 puff twice daily	January 1	5	April: Pt demonstrated adequate Diskus technique. At next follow-up assess inspiratory rate and breath-holding.
	February 1	4	
	March 1	3	
	April 2	2	
	May 1	1	
	June 2	0	

Ventolin HFA 1-2 puffs every 4-6 hours as needed for SOB/ wheeze	January 10 March 1 April 15 May 20 June 30	5 4 3 2 1	January: Pt demonstrated adequate metered- dose inhaler technique with spacer Reviewed proper cleaning of spacer
Acetaminophen 325 mg / hydrocodone 10 mg 1 tablet at bedtime as needed for pain #30	June 2	0	

Further asthma studies show his genotype is 16Arg/Arg. He was not able to produce an adequate sample for sputum testing, and his FeNO sample was contaminated with nasal NO. IgE test results are 405 U/L. Skin prick testing: (-) American elm, ragweed, Russian thistle, cockroach mix, and Dermatophagoides farina. His vital signs are blood pressure 108/90 mm Hg and heart rate 82 beat/minute. His PEF is 410 L/minute (personal best 500 L/minute). Which one of the following is most appropriate for this patient?

- A. Fluticasone/salmeterol 250/50 1 puff twice daily plus tiotropium 18 mcg once daily.
  - B. Fluticasone/salmeterol 500/50 1 puff twice daily plus mometasone 200 mcg once daily.
  - C. Fluticasone/salmeterol 500/50 1 puff twice daily plus theophylline SR 100 mg twice daily.
  - D. Fluticasone/salmeterol 250/50 1 puff twice daily plus omalizumab 375 mg every 2 weeks.
20. Two hundred patients are enrolled in a trial to determine the effect of tiotropium added to high-dose ICS plus LABA on FEV1. One-half of these patients received high-dose ICS plus LABA (control arm) and one-half received high-dose ICS plus LABA plus tiotropium (experimental arm). Results reveal patients in the experimental arm had an FEV1 improvement of 15% over the control arm group of 5%. Which one of the following represents the number of patients needed to treat with tiotropium for 1 patient to show improvement in FEV1?
- A. 1.
  - B. 10.
  - C. 100.
  - D. 1000.

## LEARNER CHAPTER EVALUATION: NEW THERAPIES IN ASTHMA.

As you take the posttest for this chapter, also evaluate the material's quality and usefulness, as well as the achievement of learning objectives. Rate each item using this 5-point scale:

- Strongly agree
  - Agree
  - Neutral
  - Disagree
  - Strongly disagree
1. The content of the chapter met my educational needs.
  2. The content of the chapter satisfied my expectations.
  3. The author presented the chapter content effectively.
  4. The content of the chapter was relevant to my practice and presented at the appropriate depth and scope.
  5. The content of the chapter was objective and balanced.
  6. The content of the chapter was free of commercial bias.
  7. The content of the chapter was useful to me.
  8. The teaching and learning methods used in the chapter were effective.
  9. The active learning methods used in the chapter were effective.
  10. The learning assessment activities used in the chapter were effective.
  11. The chapter was effective overall.

Use the 5-point scale to indicate whether this chapter prepared you to accomplish the following learning objectives:

12. Evaluate interventions based on the etiologies, status, and control of asthma.
13. Develop and justify optimal therapeutic regimens based on the underlying pathophysiology of asthma and current evidence.
14. Devise an asthma education care plan for a patient or family member(s).
15. Demonstrate an understanding of pharmacogenomic testing and how results influence treatment decisions in patients with asthma
16. Demonstrate an understanding of emerging therapies in the treatment of asthma and judge when they would be applicable in patient care
17. Display insight into technological advances in asthma care and recommend them to patients when appropriate.
18. Please expand upon any of your above responses, and/or provide any additional comments regarding this chapter:

New biologic therapies have shown promise in treating adults with severe, uncontrolled asthma, and some of these therapies are approved in the United States for children as young as age 6. However, knowledge gaps regarding the efficacy and safety of these treatments in younger children hamper our understanding of their effect on long-term outcomes.Â Introduction: The classification of asthma into phenotypes and endotypes allows for the use of targeted therapies, including three biologics which target interleukin 5 (IL-5) signaling in eosinophilic asthma. Areas covered: As of December 2016, two monoclonal antibodies, mepolizumab and reslizumab, are approved by U.S. Food and Drug Administration and one, benralizumab, is in clinical development.