Asthma

The content of In the Clinic is drawn from the clinical information and education resources of the American College of Physicians (ACP), including PIER (Physicians' Information and Education Resource) and MKSAP (Medical Knowledge and Self-Assessment Program). Annals of Internal Medicine editors develop In the Clinic from these primary sources in collaboration with the ACP's Medical Education and Publishing Division and with the assistance of science writers and physician writers. Editorial consultants from PIER and MKSAP provide expert review of the content. Readers who are interested in these primary resources for more detail can consult http://pier.acponline.org and other resources referenced in each issue of In the Clinic.

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Asthma, which is characterized by airway hyperresponsiveness and inflammation, is one of the most common respiratory illnesses. The global prevalence of asthma is increasing despite the development of new therapeutic approaches. Over the past 20 years, asthma mortality in the United States has declined; however, morbidity, as measured by hospitalizations and emergency department visits, continues to climb. Currently, about 1 in 20 Americans have asthma; in children, recent estimates suggest an incidence as high as 10%. In certain groups of Americans, such as persons of lower socioeconomic status and minority ethnicity, asthma morbidity and mortality are disproportionately high. Such trends are surprising, given the improvement in air quality in the United States and the availability of new pharmacologic therapies.

**Diagnosis**

**What symptoms or elements of clinical history are helpful in diagnosing asthma?**

Symptoms that should prompt clinicians to consider asthma are wheezing, dyspnea, cough, difficulty taking a deep breath, and chest tightness (1). Characteristically, asthma symptoms are intermittent and may remit spontaneously or with use of short-acting bronchodilators. Symptoms often vary seasonally or are associated with specific triggers, such as cold, exercise, animal dander, pollen, certain foods, aspirin or nonsteroidal anti-inflammatory drugs, or occupational exposures. Clinicians should also consider the diagnosis of asthma in all adults with chronic cough, especially if cough is nocturnal, seasonal, or related to the workplace or a specific activity.

**What physical examination findings are suggestive of asthma?**

A careful history to elicit the nature and timing of symptoms is paramount in diagnosing asthma. The physical examination is less helpful unless a patient is having an active exacerbation. The clinician should listen for wheezing during tidal respirations or prolonged expiratory phase of breathing and examine the chest for hyperexpansion. Studies suggest that respiratory signs (wheezing, forced expiratory time, accessory muscle use, respiratory rate, and pulsus paradoxus) may be useful to predict airflow obstruction, but clinicians often disagree about the presence and absence of these signs (1, 2).

The physical examination is sometimes most helpful in looking for evidence of alternative diagnoses. Persistent dry inspiratory crackles, focal wet crackles, or an abnormal cardiac examination all suggest diagnoses other than asthma.

**How can clinicians determine whether asthma is the cause of chronic cough in adults?**

Coughing may be the only manifestation of asthma in some patients (3). Up to 24% of patients presenting to a specialist with chronic cough after an initial evaluation by a primary care provider may have asthma. Although several protocols are available for the diagnosis of patients with chronic cough, it is not clear which is the best approach. Clinicians often use a trial of empirical asthma therapy, but national guidelines recommend pulmonary function tests for patients with chronic cough of unknown etiology.

**What are the indications for spirometry in a patient whose clinical presentation is consistent with asthma?**

Fair-quality evidence supports the performance of spirometry in all adult patients and older children suspected of having asthma. Initial pulmonary function testing should include spirometric measurements...
of the FEV$_1$, FVC, and the FEV$_1$–FVC ratio. If these measurements reveal airflow obstruction, then they should be repeated after administration of a bronchodilator to evaluate the reversibility of airflow obstruction. Reversibility of airflow obstruction defines asthma. Predicted normal values for spirometric measures are population-based and differ with age and ethnicity. Predictive tables are available (5, 6). Postbronchodilator improvement $\geq$ 12% of the FEV$_1$ or FVC indicates significant reversibility and therefore increases the likelihood of an asthma diagnosis.

Complete pulmonary function testing that includes lung volumes and diffusing capacity should be considered when there is evidence of a lack of airflow reversibility, or restrictive patterns with diminutions in the FEV$_1$ and FVC but a normal FEV$_1$–FVC ratio. These findings suggest chronic obstructive pulmonary disease (COPD) or interstitial lung disease (Table 1).

A number of studies show a poor correlation among the presence, severity, and timing of wheezing and the degree of airflow obstruction (7, 8). Patients vary in their degree of sensitivity to airflow limitations and can acclimate to the disability and thus become insensitive to airflow obstruction (9). Because of the disparity between patient and physician estimates of the severity of airflow obstruction and objective measures of obstruction, pulmonary function tests are important tools to characterize airflow obstruction and the degree and severity of asthma.

Spirometry should adhere to the standards of the American Thoracic Society (10). Of note, spirometry is effort-dependent, and many patients have difficulty with the FVC maneuver. In these patients (younger children, older adults, or patients with severe respiratory disease), alternative approaches, such as the FEV$_1$, may be an acceptable surrogate to the FVC, with a reduction in the FEV$_1$–FEV$_F$ ratio signifying obstruction (11).

### Table 1. Laboratory and Other Studies for Asthma

<table>
<thead>
<tr>
<th>Test</th>
<th>Notes</th>
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</thead>
<tbody>
<tr>
<td>Spirometry</td>
<td>Abnormal spirometry (reversible obstruction) can help to confirm an asthma diagnosis, but normal spirometry does not exclude asthma.</td>
</tr>
<tr>
<td>Peak flow variability</td>
<td>A patient with normal spirometry but marked diurnal variability (based on a peak flow diary kept for $&gt;2$ weeks) may have asthma, which may warrant an empirical trial of asthma medications or further testing with bronchoprovocation.</td>
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<tr>
<td>Bronchoprovocation test</td>
<td>In a patient with a highly suggestive history of asthma and normal baseline spirometry, a low PC$_{20}$ (the concentration of inhaled methacholine needed to cause a 20% drop in the FEV$_1$) on methacholine challenge testing supports a diagnosis of asthma. Cold air, exercise, and histamine are other types of provocative tests used. A normal bronchoprovocation test will almost definitively exclude asthma.</td>
</tr>
<tr>
<td>Chest radiography</td>
<td>Chest radiography may be needed to exclude other diagnoses but is not recommended as a routine test in the initial evaluation of asthma.</td>
</tr>
<tr>
<td>Complete blood count with differential</td>
<td>Although mild eosinophilia is not uncommon in persons with asthma, routine use of a CBC with leukocyte differential is not warranted in the initial evaluation.</td>
</tr>
<tr>
<td>Sputum evaluation</td>
<td>Routine sputum evaluation is not indicated for the initial evaluation of asthma.</td>
</tr>
<tr>
<td>IgE</td>
<td>Although elevated levels of IgE are not uncommon for persons with asthma, routine measurement of serum IgE is not warranted in the initial evaluation.</td>
</tr>
<tr>
<td>Quantitative IgE antibody assays</td>
<td>There is a strong association between allergen sensitization, exposure, and asthma. Allergy testing is the only reliable way to detect the presence of specific IgE to indoor allergens. Skin testing (or in vitro testing) may be indicated to guide the management of asthma in selected patients, but results are not useful in establishing the diagnosis of asthma.</td>
</tr>
</tbody>
</table>

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Does normal spirometry rule out a diagnosis of asthma?
Abnormal spirometry (reversible obstruction) can confirm an asthma diagnosis, but normal spirometry does not rule out asthma. Clinicians should consider further studies in patients with normal spirometry who have a clinical history suggestive of asthma (Table 1). Bronchoprovocation with methacholine or histamine can be helpful in establishing a diagnosis in patients who report that they only have symptoms during exercise or at certain times of the year. Alternatively, marked diurnal variability based on measurements recorded in a peak flow diary kept for at least 2 weeks can help to establish asthma as the cause of symptoms. However, peak flow measurements are highly effort-dependent and may offer no opportunity for quality assurance of their accuracy.

When should clinicians consider provocative pulmonary testing?
A gold standard for diagnosis of asthma remains elusive. However, methacholine hyperresponsiveness in the pulmonary function laboratory has high reproducibility and accepted standardization (12). The test is safe but requires sophisticated instrumentation and is labor-intensive and expensive. In a patient with symptoms suggestive of asthma who has normal baseline spirometry, a low $PC_{20}$ (the concentration of inhaled methacholine needed to induce a 20% decrease in the FEV$_1$) on methacholine challenge testing supports the diagnosis. Studies of methacholine challenge suggest that it is sensitive and has a high negative predictive value for the diagnosis of asthma (13, 14). Although cold air and exercise have been used in research to define mechanisms of bronchoconstriction, methacholine challenge remains the provocative test of choice in patients with normal pulmonary function tests who have symptoms consistent with asthma.

Spirometry before, during, or after exercise may be the only method to document bronchoconstriction in patients with exercise-induced asthma. As an alternative, monitoring peak flow is easy and inexpensive, but the measurement is less precise and limited in reproducibility and sensitivity (15). Because spirometry and peak flow have limitations in sensitivity and specificity, they are probably best used as part of a diagnostic strategy in conjunction with a comprehensive history, physical examination, and other laboratory data (16).

How should clinicians classify asthma severity?
The National Heart Lung and Blood Institute (NHLBI) Expert Panel Report 2 (2) defines asthma severity according to symptoms and spirometric measurements. As shown in Table 2, asthma severity is classified as intermittent, mild, moderate, and severe persistent. Each category is defined by the frequency of rescue inhaler use as well as nocturnal symptoms in conjunction with the FEV$_1$, PEFR measurement. It is important to note that decrease in FEV$_1$ correlates with airflow obstruction and not with changes due to restrictive lung disease.

The initial determination of asthma severity should be made when the patient is receiving no medications. Asthma severity is dynamic—for example, patients who were initially diagnosed as having severe persistent asthma may have symptoms consistent with mild persistent asthma while receiving medication. The NHLBI Expert Panel Report 2 (2) suggests annual spirometry to aid in the classification of asthma, but high-quality studies are not available to support this recommendation.
What comorbid conditions and alternative diagnoses should clinicians consider in patients with suspected asthma?

The differential diagnosis of asthma includes the following conditions: COPD, interstitial lung disease, vocal cord dysfunction, congestive heart failure, medication-induced cough, bronchiectasis, pulmonary infiltration with eosinophilia syndromes, obstructive sleep apnea, mechanical airway obstruction, cystic fibrosis, and pulmonary hypertension. Clinicians should consider one of these alternative diagnoses when asthma is difficult to control or if the patient has atypical signs and symptoms. These conditions can also coexist in a patient who has asthma.

An important difference between asthma and COPD is the history of smoking. Although 30% of patients with asthma in the United States smoke, COPD, manifested by chronic bronchitis and emphysema, often occurs in older persons with a substantial history of cigarette smoking. Patients with COPD also do not demonstrate reversibility with bronchodilators on pulmonary function testing.

Lung imaging with radiography or computed tomography is helpful in identifying bronchiectasis or lung masses. Echocardiography can help to identify cardiovascular disorders, including ischemic heart disease, ventricular dysfunction, and pulmonary hypertension. Flow-volume loops and direct visualization of the larynx during an acute episode are useful in evaluating patients for vocal cord paralysis.

Chronic cough and dyspnea or recurrent wheezing are common signs of COPD, vocal cord dysfunction, cystic fibrosis, obstructive sleep apnea, Churg-Strauss syndrome, allergic bronchopulmonary aspergillosis, interstitial lung disease, bronchiectasis, congestive heart failure, and pulmonary hypertension, or may be side effects of...
Measures to Reduce Dust Mite and Other Environmental Allergen and Irritant Exposure

- Use air conditioning to maintain humidity <50%
- Remove carpets
- Limit fabric household items, such as upholstered furniture, drapes, and soft toys
- Use impermeable covers for mattresses and pillows
- Launder bedding weekly in water at least 130°F
- Ensure adequate ventilation—may be the only measure necessary for dust mite control in dry climates
- Exterminate to reduce cockroaches
- Remove cats from the home
- Reduce dampness in the home
- Avoid wood-burning or unvented gas fireplaces or stoves
- Avoid tobacco smoke

CLINICAL BOTTOM LINE

Diagnosis... A careful history focusing on the nature and timing of symptoms (wheezing, dyspnea, cough, chest tightness) and potential triggers is essential to the diagnosis of asthma. Moderate-quality evidence supports the use of spirometry in assessment of all adult patients and older children suspected of having asthma. However, normal spirometry does not definitively rule out asthma. Clinicians should consider provocative pulmonary testing for patients with normal spirometry but characteristic symptoms and no evidence of alternative diagnoses.

What evidence supports the use of indoor air-cleaning devices for patients with asthma?

One study considered associations between indoor air pollutants and symptoms in 164 adults with asthma and found an increase in days of restricted activity (odds ratio [OR], 1.61 [95% CI, 1.06 to 2.46]) and greater likelihood of increased asthma symptoms in patients exposed to a smoker at home (OR, 2.05 [CI, 1.79 to 2.40]) (20).

CLINICAL BOTTOM LINE

What advice about reducing allergen exposure should clinicians give patients?

Avoidance of triggers is the cornerstone of nonpharmacologic therapy of asthma. Clinicians should question the patient about triggers and provide strategies to diminish exposure to them (see box). Since many patients with asthma are atopic, reducing exposure to allergens can improve outcomes. Other common triggers of asthma include aspirin, nonsteroidal anti-inflammatory drugs, and sulfites in food preservatives. Limiting exposure to triggers is difficult to implement or sustain in some patients; however, in most cases such triggers are dose-dependent, so even modest remediation can be beneficial.

The NHLBI Expert Panel Report recognized environmental smoke exposure as a common cause of asthma exacerbations (2), and several studies have impugned active and passive cigarette smoking as a cause of decreasing lung function in adult cigarette smokers (18, 19).
Household humidity below 50% with dehumidifiers or air conditioners reduces dust mites and mold (21).

A multidisciplinary committee convened by the Institute of Medicine reviewed available evidence concerning the impact of ventilation and air cleaning on asthma (21). Although they concluded that particle air cleaning may reduce symptoms in certain situations, evidence is inadequate to broadly recommend air cleaning for patients with asthma.

How should clinicians select from among available drug therapy for asthma?

Table 3 summarizes drugs available to treat asthma. Table 4 presents a stepwise approach to using these drugs to maximize control of symptoms (2, 22).

Clinicians should tailor drug therapy to the severity of asthma (Table 2). Stepwise therapy consists of agents for acute relief of symptoms (rescue therapy) and for long-term control. Rescue therapy is critically important regardless of asthma severity. Patients with persistent symptoms require long-term control in addition to rescue therapy. If control is poor, stepping up to more intense therapy is indicated. If symptoms are well-controlled, stepping down to less intensive therapy is indicated.

Clinicians should review therapy every 1 to 6 months, depending on asthma severity. Asthma is a chronic disease that often requires long-term therapy. Given the complexity of airway inflammation, multiple drugs with different actions against the various aspects of the inflammatory response are often necessary.

Rescue Therapy

Patients with mild intermittent asthma may only need a quick relief medication (short-acting β-agonists) on an as-needed basis. Short-acting β-agonists are the drugs of choice for reversal of acute bronchospasm and are safe and well-tolerated. Patients with persistent asthma (mild, moderate, or severe) should also receive a short-acting β-agonist and advice to keep the medication readily available for relief of acute symptoms.

Long-Term Controller Therapy

Patients with mild, moderate, or severe persistent asthma have abnormal baseline pulmonary function and require long-term controller therapy. Patients with mild persistent asthma should receive 1 long-term controller medication, usually a low-dose inhaled corticosteroid.

Compared with patients with mild intermittent asthma, patients with mild persistent asthma are more prone to underlying inflammation and disease exacerbations. Low-dose inhaled corticosteroids have been shown to reduce bronchial hyperresponsiveness, reduce rescue β-agonist use, and control symptoms. Secondary alternatives to inhaled corticosteroids are leukotriene-receptor antagonist medications (e.g., montelukast, zafirlukast) or cromolyn.

Patients with moderate persistent asthma will probably require 1 or 2 long-term controller medications in addition to short-acting rescue therapy. The therapy of choice in this group includes low-dose inhaled corticosteroids and a long-acting β-agonist or a moderate dose of a single long-term controller medication. Evidence suggests that patients who remain symptomatic while taking moderate doses of inhaled corticosteroids benefit from the addition of a long-acting bronchodilator such as theophylline, salmeterol, or formoterol. The additive effect of the long-acting bronchodilator improves lung physiology, decreases use of rescue β-agonists, and reduces symptoms better than doubling the dose of an inhaled corticosteroid (23–26).

However, there is little evidence to guide the best choice of combinations. Clinicians and patients must weigh the reduced risk for adverse effects of steroids against the use of more complicated regimens. It is

Evidence is inadequate to broadly recommend air cleaning devices for patients with asthma.

<table>
<thead>
<tr>
<th>Class/Agent</th>
<th>Mechanism of Action</th>
<th>Benefits</th>
<th>Side Effects</th>
<th>Notes</th>
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<tbody>
<tr>
<td>Short-acting β-agonists:</td>
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<tr>
<td>Albuterol</td>
<td>Relaxes bronchial smooth muscle, improves airflow</td>
<td>Fastest improvement in airflow physiology of all anti-asthma medications</td>
<td>Tachycardia, palpitations, tremors, hypokalemia</td>
<td>Should be carried by all patients with asthma at all times. Drug class of choice for acute bronchospasm. Use only as needed. Effective at preventing symptoms of asthma when used before exercise. Assessment of quantity of β-agonist use may identify patients who require a &quot;step-up&quot; in therapy. Use of &gt;1 canister during a 1-month period suggests inadequate control. Oral preparations available, but inhaled is preferred due to better side effect profile.</td>
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<tr>
<td>Metaproterenol</td>
<td>Improves airflow physiology, reduced need for rescue medications (short-acting β-agonists), prevents exacerbations and hospitalizations</td>
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<td>Local: cough, dysphonia, and thrush. Systemic: cortisol suppression, adrenal suppression, potential osteoporosis, cataracts, glaucoma</td>
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<td>Terbutaline</td>
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<td>Pirbuterol</td>
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<td>Inhaled corticosteroids:</td>
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<tr>
<td>Beclomethasone dipropionate</td>
<td>Anti-inflammatory, blocks late reaction to allergen, and reduces airway hyperresponsiveness</td>
<td>Improved airflow physiology, reduced need for rescue medications (short-acting β-agonists),</td>
<td>Local: cough, dysphonia, and thrush. Systemic: cortisol suppression, adrenal suppression, potential osteoporosis, cataracts, glaucoma</td>
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<tr>
<td>Beclomethasone hydrofluoroalkane</td>
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<td>Budesonide</td>
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<td>Flunisolide</td>
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<td>Fluticasone propionate</td>
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<td>Triamcinolone acetonide</td>
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<td>Ciclesonide</td>
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<td>Mometasone</td>
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<tr>
<td>Long-acting inhaled β-agonists:</td>
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<tr>
<td>Salmeterol</td>
<td>Smooth muscle relaxation</td>
<td>Improved a.m. peak flow, improved nocturnal symptoms, effective in preventing symptoms of exercise-induced asthma for up to 12 hours after a single dose</td>
<td>Tachycardia, skeletal muscle tremor, prolongation of QT interval in overdose</td>
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<td>Formoterol</td>
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<tr>
<td>Combined fixed-agent controllers:</td>
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<tr>
<td>Fluticasone and salmeterol</td>
<td>Anti-inflammatory moiety blocks late reaction to allergen, and reduces airway hyperresponsiveness, and long-acting β-agonist leads to smooth muscle relaxation</td>
<td>Improved airflow physiology, reduced need for short acting β-agonists, prevents exacerbations and hospitalizations; improved a.m. peak flow, improved nocturnal symptoms</td>
<td>Dysphonia, thrush, nausea, headaches</td>
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<td>Budesonide and formoterol</td>
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<td>Leukotriene modifiers:</td>
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<tr>
<td>Montelukast</td>
<td>Work by inhibition of synthesis or antagonism of receptor site for cysteinyl leukotrienes</td>
<td>Improvements in symptoms and pulmonary function, decreased exacerbation rate, reduced need for rescue β-agonist</td>
<td>Transient elevation in liver enzymes occurs with Zileuton and mandates monitoring of liver enzymes with initiation of therapy; there is controversy over possible link with Churg-Strauss angitis (causation has not been established)</td>
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<tr>
<td>Zafirlukast</td>
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<td>Zileuton</td>
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<tr>
<td>Theophylline</td>
<td>Smooth muscle relaxation, may have secondary effects of inhibiting airway inflammation and enhancing diaphragm contractility</td>
<td>Modest improvement in expiratory flow rates</td>
<td>Dose-related acute toxicities include tachycardia, nausea vomiting, tachyarrhythmias (SVT), CNS stimulation, headache, seizures. Sometimes adverse effects are seen at therapeutic levels</td>
<td>Studies show a benefit in the addition of theophylline to inhaled corticosteroids</td>
</tr>
</tbody>
</table>
### Table 3. Drug Treatment for Asthma (continued)

<table>
<thead>
<tr>
<th>Class/Agent</th>
<th>Mechanism of Action</th>
<th>Benefits</th>
<th>Side Effects</th>
<th>Notes</th>
</tr>
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<tbody>
<tr>
<td>Mast cell stabilizers:</td>
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<tr>
<td>Cromolyn</td>
<td>Anti-inflammatory, blocks early and late reaction to allergens, and stabilizes mast cell membranes; inhibits eosinophil activation and mediator release</td>
<td>Improved airflow physiology, reduced need for rescue medications (short-acting β-agonists), prevents exacerbations</td>
<td>Cromolyn: no significant side effects</td>
<td>The therapeutic response to this class of drugs is less predictable than to corticosteroids, but they continue to be used due to their safety profile</td>
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<td>Nedocromil</td>
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<td>Systemic corticosteroids:</td>
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<tr>
<td>Prednisone</td>
<td>Anti-inflammatory, blocks late reaction to allergen, and reduces airway hyperresponsiveness</td>
<td>Improved airflow physiology, reduced need for rescue medications (short-acting β-agonists), prevents exacerbations and hospitalizations</td>
<td>Short-term: increased appetite and weight gain, fluid retention, reversible abnormalities in glucose metabolism, mood alterations Long-term: dermal thinning, cortical suppression, adrenal suppression, hypertension, diabetes mellitus, osteoporosis, avascular necrosis of femoral head, cataracts, glaucoma</td>
<td>Most effective medication for severe exacerbations and long-term control for patients with severe persistent asthma who are otherwise uncontrolled. Always seek lowest possible effective dose. Patients on corticosteroids (either daily or at least 2 corticosteroid prescriptions for 5-10 days/yr) and undergoing surgery or with acute severe illness should be assessed for adrenal reserve or treated presumptively with short-term systemic corticosteroid. Studies show that it is safe to give a short course of oral corticosteroids (7-10 days) without tapering.</td>
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<td>Prednisolone</td>
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<td>Methylprednisolone</td>
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<td>Triamcinolone</td>
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<td>Anticholinergic agents:</td>
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<tr>
<td>Ipratropium bromide</td>
<td>Bronchodilation mediated by antagonism of muscarinic receptors of airway smooth muscle</td>
<td>Improved airflow physiology</td>
<td>Blurred vision if contact with eyes, dry mouth and respiratory symptoms</td>
<td>Treatment of choice in β-blocker induced bronchospasm; may give added bronchodilation to β-agonists. Meta-analysis of the use of ipratropium bromide in the treatment for acute severe asthma shows that there is a modest physiologic benefit in the addition of ipratropium to albuterol, with negligible risk of adverse side effects. Tiotropium has been suggested as an alternative to long-acting β-agonists, but suitable effectiveness studies are lacking.</td>
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<td>Glycopyrrolate etopium</td>
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<tr>
<td>Intravenous magnesium sulfate</td>
<td>Smooth muscle relaxation</td>
<td>Brachodilatation in acute severe asthma failing to respond to nebulized bronchodilators-</td>
<td>Minor effects; flushing, lethargy, nausea, or local reaction at the IV site</td>
<td></td>
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<tr>
<td>Omalizumab</td>
<td>A monoclonal antibody that binds to IgE in patients aged 12 years or older with moderate to severe persistent asthma, proven IgE-mediated sensitivity to perennial aeroallergens, and poor response to standard treatment. Binding of IgE by monoclonal antibody inhibits binding to high-affinity IgE receptors on mast cells and basophils</td>
<td>Reduction in exacerbations in patients with severe persistent asthma on the best available therapy</td>
<td>The main danger is anaphylaxis. Injections should be administered by trained personnel, and patients should be observed for 2 hours after every injection. Anaphylaxis has been reported up to 24 hours after injection, and patients receiving omalizumab treatment should be fully prepared to begin treatment for anaphylaxis with an epinephrine autoinjector</td>
<td>Anaphylaxis may occur after any dose of omalizumab (including the first dose), even if there was no adverse reaction to the first dose. The symptoms and signs of anaphylaxis include bronchospasm, hypotension, syncope, urticaria, and angioedema of the throat or tongue. In the major trials, there was a small increase in new or recurrent cancer compared to the control group.</td>
</tr>
</tbody>
</table>

*Readers can access detailed information on dosing in PIER at http://pier.acponline.org/physicians/diseases/d146/drug.tx/d146-s7.html. CNS = central nervous system; FDA = Food and Drug Administration*

Unclear whether controlling the disease with high-dose inhaled corticosteroids or moderate-dose inhaled corticosteroids plus a long-acting bronchodilator results in a better long-term outcome.

In a 12-week, randomized, controlled trial of 447 patients who remained symptomatic on treatment with inhaled corticosteroids, a dry-powder inhaler containing salmeterol and fluticasone was more effective in improving physiologic endpoints, reducing rescue therapy use, and reducing exacerbations...
**Table 4. Stepwise Approach for Managing Asthma in Adults**

<table>
<thead>
<tr>
<th>STEP Classification</th>
<th>Long-Term Control</th>
<th>Quick Relief</th>
<th>Education</th>
</tr>
</thead>
<tbody>
<tr>
<td>Step 1: Mild intermittent</td>
<td>No daily medication needed</td>
<td>Short acting bronchodilator: inhaled β₂-agonists* as needed for symptoms</td>
<td>Teach basic facts about asthma; teach inhaler/spacer/holding chamber technique; discuss roles of medications; develop self-management plan; develop action plan for when to take rescue medications, especially for patients with a history of severe exacerbations; discuss appropriate environmental control measures to avoid exposure to known allergens and irritants</td>
</tr>
<tr>
<td>Step 2: Mild persistent</td>
<td>One daily medication: • Anti-inflammatory*: either inhaled corticosteroid (low doses) or cromolyn* or nedocromil* (children usually begin with a trial of cromolyn or nedocromil) • Sustained-release theophylline to serum concentration of 5–15 µg/mL is an alternative, but not preferred, therapy. • Montelukast, zafirlukast, or zileuton may also be considered for patients age 12 and older, although their position in therapy is not fully established</td>
<td>Short-acting bronchodilator: inhaled β₂-agonists* as needed for symptoms</td>
<td>Step 1 actions, plus teach self-monitoring; refer to group education if available; review and update self-management plan</td>
</tr>
<tr>
<td>Step 3: Moderate persistent</td>
<td>Preferred treatment: • Low-to-medium dose inhaled corticosteroids and long-acting inhaled β₂-agonists. Alternative treatment: Increase inhaled corticosteroids within medium-dose range OR • Low-to-medium dose inhaled corticosteroids and either leukotriene modifier or theophylline. OR • If needed (particularly in patients with recurring severe exacerbations): Increase inhaled corticosteroids within medium-dose range, and add long-acting inhaled β₂-agonists. Alternative treatment: Increase inhaled corticosteroids to medium-dose range, and add either leukotriene modifier or theophylline</td>
<td>Short-acting bronchodilator: inhaled β₂-agonists* as needed for symptoms</td>
<td>Step 1 actions, plus teach self-monitoring; refer to group education if available; review and update self-management plan</td>
</tr>
<tr>
<td>Step 4: Severe persistent</td>
<td>Preferred treatment: HIGH-dose inhaled corticosteroids AND Long-acting inhaled β₂-agonists AND, if needed, Corticosteroid tablets or syrup long-term (2 mg/kg/d, generally do not exceed 60 mg/d). (Make repeated attempts to reduce systemic corticosteroids and maintain control with high-dose inhaled corticosteroids.)</td>
<td>Short-acting bronchodilator: inhaled β₂-agonists* as needed for symptoms.</td>
<td>Step 2 and 3, plus refer to individual education/counseling</td>
</tr>
</tbody>
</table>

*Intensity of treatment depends on severity of exacerbation. Use of short-acting inhaled β₂-agonists on a daily basis, or increasing use, indicates the need for additional long-term control therapy.

Long-acting β-agonists may help improve asthma symptoms, but they may also increase risks for adverse outcomes. Patients started on these medications should be followed closely.

A meta-analysis of 19 randomized, controlled trials found that, compared with placebo, long-acting β-agonists increased severe exacerbations requiring hospitalization (OR, 2.6 [CI, 1.6 to 4.3]), life-threatening exacerbations (OR, 1.8 [CI, 1.1 to 2.9]), and asthma-related deaths (OR, 3.5 [CI, 1.3 to 9.3]; risk difference, 0.07%) (28). Risks were similar for salmeterol and formoterol and in children and adults. Several trials did not report information about potential harms, and the number of reported deaths was small. Black patients and patients not using inhaled corticosteroids seemed to be at high risk for these outcomes. These results suggest that long-acting β-agonists should not be used alone in asthma (28).
Patients with severe persistent asthma may require 3 controller medications to adequately control symptoms. Patients with this level of disease are extremely prone to exacerbations and have profound underlying inflammation. Direct comparisons of high-dose inhaled corticosteroids to leukotriene-receptor modifiers (such as montelukast) revealed that the inhaled corticosteroids were more effective. The addition of montelukast to the regimen of a patient requiring high-dose inhaled corticosteroids, however, allowed a significant reduction in the dose of the inhaled corticosteroid while maintaining asthma control (29).

In a randomized, controlled study of patients with inadequate symptom control despite low- to moderate-dose inhaled corticosteroid, the addition of montelukast improved FEV1, daytime symptoms and nocturnal awakenings (30).

A systematic review of trials comparing the addition of daily leukotriene-receptor antagonists or long-acting β-agonists to inhaled corticosteroids in patients with severe asthma concluded that long-acting β-agonists were better than leukotriene antagonists in preventing the need for rescue therapy and systemic steroids and improved lung function and symptoms (31, 32).

Omalizumab is a monoclonal antibody that binds to IgE that has been shown to reduce exacerbations in patients with severe persistent asthma despite best available therapy (33). However, severe anaphylaxis has been reported up to 24 hours after injection. Clinicians should view the drug as an option only in carefully selected cases of severe persistent asthma in patients with proven IgE-mediated sensitivity to perennial aeroallergens, and failure of other therapeutic options.

What therapeutic options are effective for patients with exercise-induced asthma?

In some patients, exercise exacerbates asthma. Symptoms often occur with vigorous exercise in cold, dry air. Patients who have more than 2 episodes of exercise-induced asthma per week are candidates for intervention. Patients who have normal baseline pulmonary function but experience exercise-induced symptoms can be treated effectively with albuterol, cromolyn sodium, or nedocromil 15 to 30 minutes before exercise.

If exercise-induced symptoms persist, addition of long-acting bronchodilators or leukotriene antagonists may be helpful. Recent evidence suggesting that monotherapy with long-acting bronchodilators may cause adverse outcomes in asthma cautions against using these agents as monotherapy in exercise-induced asthma (28, 34). Despite these concerns, evidence clearly suggests that formoterol or salmeterol is more effective than placebo in preventing exercise-induced bronchoconstriction (35, 36). In a study of patients with mild stable asthma, once-daily treatment with montelukast protected against exercise-induced bronchospasm (37).

The clinician should consider exercise-induced asthma in the context of the patient’s overall therapy. Many patients who present with putative exercise-induced asthma may have abnormal pulmonary function tests at baseline. Such patients should be treated according to the NHLBI Expert Panel Report 2 regimen (2).

When should primary care clinicians refer patients with asthma to a specialist for treatment?

Although definitive evidence about the effect of specialty care on asthma outcomes is not available, according to consensus recommendations referral to a specialist may be useful in the following clinical situations:

• History of life-threatening exacerbations
• Atypical signs and symptoms
• Severe persistent asthma
• Need for continuous oral corticosteroids or high-dose inhaled steroids or more than 2 courses of oral steroids in a 1-year period

29. Ducharme FM, Lasserson TJ, Cates CJ. Long-acting通俗 β2-agonists versus anti-leukotrienes as add-on therapy to inhaled corticosteroids for chronic asthma. Cochrane database Syst Rev. 2006;CD003137. [PMID: 17054161]
• Comorbid conditions that complicate asthma diagnosis or treatment
• Need for provocative testing or immunotherapy
• Problems with adherence or allergen avoidance
• Unusual occupational or other exposures.

Whether to consult an allergist or pulmonologist should reflect local availability and consideration of the predominant comorbid conditions and complicating features in asthma. For example, a patient with sleep apnea and asthma may benefit from a pulmonary consultation, whereas the patient who has asthma with an atopic component may benefit from referral to an allergist.

When is hospitalization indicated for a patient with asthma?
Patients who have a sustained response to treatment in outpatient settings do not need to be hospitalized if they understand the importance of continued anti-inflammatory therapy and close follow-up. The decision to hospitalize a patient with asthma should consider patient characteristics, severity of disease, and initial response to short-term therapy. Patients with an incomplete response to therapy during an exacerbation (PEFR >50% but <70% than patient’s best or of the predicted value) may need hospitalization. When posttreatment PEFR remains <50% of the predicted value, intensive care unit admission may be warranted. However, data are insufficient to support the idea that adequate oxygen saturation and PEFR at the time of emergency department discharge predict a good outcome.

In a prospective cohort study of adults presenting with asthma to urban emergency departments in the United States, the PEFR of those who had a relapse did not significantly differ from those who did not have a relapse after discharge from the emergency department. However, such historical features as emergency department or urgent care visits (OR, 1.3 per 5 visits), use of a home nebulizer (OR, 2.2), multiple triggers (OR, 1.1 per trigger), and longer duration of symptoms (OR, 2.5 for 1 to 7 days) did predict relapse (38).

Factors Associated with Poor Outcomes of Asthma Exacerbations

- Prior intubation
- Multiple asthma-related exacerbations
- Emergency room visits for asthma in the previous year
- Nonuse or low adherence to inhaled corticosteroids
- History of depression, substance abuse, personality disorder, unemployment, or recent bereavement

What factors identify patients with asthma at high risk for fatal or near-fatal events during an exacerbation?

Historical factors reflect the risk for fatal and near-fatal asthma-related events and should lower the threshold for hospitalization of a person when these factors are present. Such factors include asthma history, socioeconomic characteristics, and comorbid conditions (see Box).

How often should clinicians see patients with asthma for routine follow-up?
No definitive studies are available to guide the frequency of asthma follow-up, but consensus suggests that for patients with newly diagnosed asthma, 2 to 4 visits during the 6 months after diagnosis can help to establish and reinforce the patient’s basic knowledge and management skills. For patients with asthma who have shown maximum improvement in pulmonary function and have minimal to no related symptoms, the NHLBI Expert Panel Guide suggests routine follow-up every 1 to 6 months with annual pulmonary function tests (2); however, evidence documenting the benefit of this strategy is limited. The Report also suggests follow-up within 7 days for patients discharged from the hospital and within 10 days for patients treated as outpatients for an exacerbation. Studies have shown that relapse occurs in about 1% of patients per day until the follow-up visit (38–40).
What do professional organizations recommend regarding the care of patients with asthma?

Many of the recommendations provided in this overview are from a guideline developed by the NHLBI that was most recently updated in 2002 (22). The guidelines were approved by the 40 organizations that comprise the National Asthma Education and Prevention Program. The document covers pathogenesis, medications, monitoring, and prevention and is available free at www.nhlbi.nih.gov/guidelines/asthma/asthgdln.htm.

Numerous other organizations have developed recommendations related to the care of patients with asthma, including the American Academy of Asthma, Allergy and Immunology (www.aaaai.org); the American Lung Association (www.lungusa.org); and the Asthma and Allergy Foundation of America (www.aafa.org). These organizations also provide demographically and culturally sensitive educational programs and teaching tools.

What is the role of patient education in optimizing the outcome of asthma care?

Asthma is a paradigm illness for patient self-management because of its intermittent and unpredictable nature. Patients and family members can recognize changes and initiate specific actions to minimize exacerbations. Clinicians should include asthma education as part of each office visit, and formal asthma education programs may be particularly helpful for patients who have had asthma hospitalizations, emergency department visits, or frequent exacerbations. Important elements of asthma education include basic information, the role of medications, inhaler and peak flow meter skills, environmental control measures, and appropriate use of rescue medications. Demographically and culturally appropriate educational materials can be used as an adjunct to one-on-one asthma education.

Because many patients use metered-dose inhalers improperly, all patients should receive instruction on proper use.

Clinicians should develop individualized self-management plans for all patients, taking into consideration underlying disease severity and the patient's willingness and ability to manage the illness. For patients with mild disease, clinicians should consider providing a simple self-management plan that provides information on how to handle exacerbations, including health care contacts in case of emergency. For patients with moderate-to-severe disease, provide a self-management plan that incorporates a daily diary and a detailed written action plan with specific objective and subjective targets.

CLINICAL BOTTOM LINE

Practice Improvement

Treatment... Patients should avoid asthma triggers. While air conditioners or dehumidifiers may be helpful, indoor air-cleaning devices are of unclear utility. All patients with asthma should have short-acting β-agonists available for relief of acute symptoms. For patients with persistent asthma, treatment with long-term controller medications should begin with low-dose inhaled corticosteroids and be stepped up to higher doses and/or additional agents according to asthma severity. Patients with severe persistent asthma may need as many as 3 long-term controller medications.
Should all patients with asthma receive peak flow meters?
The precision of patients and physicians in estimating the degree of airflow obstruction based on symptoms alone varies greatly, so objective measurement of expiratory flow rates could in theory be useful to guide therapeutic strategies. However, studies that have randomly assigned patients to action plans that incorporate PEFR have not shown major improvements compared with action plans based on symptoms alone (41, 42).

Clinicians should ensure that all patients with persistent moderate-to-severe asthma have a peak flow meter at home and know how to use it. If patients are unwilling to measure peak flow, provide instruction in symptom-based monitoring.

Do U.S. stakeholders consider asthma care when evaluating the quality of care a physician delivers?
In April 2005, The Ambulatory Care Quality Alliance (AQA) released a set of 26 health care quality indicators for clinicians, consumers, and health care purchasers to use in quality improvement efforts, public reporting, and pay-for-performance programs (www.ahrq.gov/qual/aqastart.htm). In May 2005, the Centers for Medicare & Medicaid Services (CMS) endorsed the development of these indicators. Of the 26 AQA indicators, 2 focus on asthma care (see the Box).

As part of CMS’s Physician Quality Reporting Initiative, physicians who successfully report a designated set of quality measures on claims for services provided July 1 to December 31, 2007, may earn a bonus payment. See the Box for the 2 CMS measures related to asthma care (www.cms.hhs.gov/specifications_2007-02-04.pdf).

Ambulatory Care Quality Alliance Performance Measures for Asthma
• Percentage of individuals who were identified as having persistent asthma during the 1 year before the measurement year and who were appropriately prescribed asthma medications (e.g., inhaled corticosteroids) during the measurement year.
• Percentage of individuals with mild, moderate, or severe persistent asthma who were prescribed either the preferred long-term control medication (inhaled corticosteroid) or an acceptable alternative treatment.

Center for Medicare & Medicaid Services (CMS) Asthma Quality Measures
• Percentage of patients aged 5 to 40 years with a diagnosis of mild, moderate, or severe persistent asthma who were prescribed either inhaled corticosteroid or an acceptable alternative.
• Percentage of patients aged 5 to 40 years with a diagnosis of asthma who were evaluated during at least one office visit within 12 months for the frequency (numeric) of daytime nocturnal asthma symptoms.

in the clinic
Tool Kit

Asthma

http://PIER.acponline.org
Asthma module of PIER, an electronic decision support resource designed for rapid access to information at the point of care.

http://pennhealth.com/ency/presentations/100200_1.htm
Tutorial on proper use of metered dose inhalers.

http://pier.acponline.org/qualitym/asm.html
Tool to assist clinicians in developing strategies to improve adherence to the AQA asthma performance measures.

www.annals/intheclinic/tools
Download copies of the patient information sheet that appears on the following page for duplication and distribution to your patients.
Asthma causes a squeezing of the muscle in the walls of the tubes (airways, bronchi) that bring air to the lungs. Breathing becomes difficult when this happens.

**HEALTH TIPS* WHAT YOU CAN DO**

Here’s what you can do to feel better.

Stay away from what makes your asthma worse:
- Dust
- Smoke
- Animals
- Cold or dry air

Don’t smoke and stay away from people who do

Asthma-proof your home:
- Get special mattress and pillow covers
- Get rid of old carpets and drapes
- Use air conditioners and dehumidifiers

Use your medicines the right way:
- Take medicines that prevent attacks every day
- Take medicines that stop attacks when you need them
- Learn the right way to use your inhalers

Call your doctor or go to the hospital if it is hard to breathe and your medicines are not helping

**Things to ask your doctor:**

Which medicines are to keep attacks from happening?

Which medicines are to stop attacks when they come on?

Can you show me the right way to use my inhaler?

Can I use my inhalers more often if I need to?

What are the side effects of my inhalers and my other medicines?

Do I need a special meter to check my breathing at home? How do I use it?

How long should I wait to call the doctor or go to the hospital if I am having trouble breathing?

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Asthma makes you cough and wheeze and can make it hard to breathe.

**Web Sites with Good Information about Asthma**

**MedlinePLUS**
www.nlm.nih.gov/medlineplus/asthma.html

**American Lung Association**
www.lungusa.org

**How to Use a Metered Dose Inhaler**

Inhalers deliver a specific dose of medicine to the lungs in a spray form.

1. Take off the cap and shake the inhaler hard.
2. Breathe out all the way.
3. Hold the inhaler about 2-fingers width from your mouth.
4. Start to breath in slowly through your mouth as you press down on the inhaler once and keep breathing in slowly until you can’t breathe in any more.
5. Hold your breath and count to 10 slowly.
6. Repeat steps 1 to 5 if your doctor has prescribed more than 1 puff of medicine, wait about 1 minute between puffs.

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*HEALTH TIPS are developed by the American College of Physicians Foundation and PIER*
CME Questions

1. A 46-year-old woman with persistent asthma is evaluated in the clinic for a scheduled follow-up visit. Since her most recent visit 6 months ago, her disease has been stable on a regimen of high-dose inhaled corticosteroids plus a long-acting β-agonist and as-needed albuterol, which she uses approximately once every 1 to 2 weeks. The patient is pleased with the current therapy, and the as-needed albuterol is continued.

Which of the following would be the best approach to this patient’s therapy?
A. Continue inhaled corticosteroids and the long-acting β-agonist at current doses
B. Discontinue inhaled corticosteroids and the long-acting β-agonist
C. Continue the long-acting β-agonist and reduce the dose of inhaled corticosteroids
D. Discontinue the long-acting β-agonist and reduce the dose of inhaled corticosteroids

2. A 75-year-old woman with a long-standing history of asthma is evaluated for increased nocturnal asthma symptoms and frequent need to use an albuterol inhaler. Her treatment regimen now consists of daily moderate-dose inhaled corticosteroids.

On physical examination she has occasional wheezing; the examination is otherwise unremarkable. Office spirometry shows an FEV1 of 2.2 L (75% of predicted).

Which of the following is the most appropriate adjustment to this patient’s therapy?
A. Double the inhaled corticosteroid dose
B. Add theophylline
C. Add a leukotriene-receptor antagonist
D. Add a long-acting β-agonist
E. Add anti-IgE antibody

3. A 38-year-old woman is evaluated for worsening control of mild persistent asthma. Her disease had been under good control on therapy with moderate-dose inhaled corticosteroids plus as-needed albuterol until 6 weeks ago when she had an acute respiratory tract infection. Since then she has had significant worsening of her symptoms, with nightly cough and wheezing. She uses an albuterol rescue inhaler 6 to 8 times per day.

Which of the following is the most appropriate therapy for this patient?
A. A 7-day course of a fluoroquinolone antibiotic
B. Nebulized albuterol–ipratropium bromide at home
C. A short course of oral corticosteroid therapy
D. A leukotriene-receptor antagonist

4. A 28-year-old man is evaluated for a 6-month history of episodic dyspnea, cough, and wheezing. He had asthma as a child but has been asymptomatic since his early teens. The recent symptoms, which began after an upper respiratory tract infection, are often triggered by exercise or exposure to cold air and awaken him from sleep 3 or 4 times per month.

On physical examination, vital signs are normal. There is scattered wheezing in both lung fields. Office spirometry shows an FEV1 of 2.2 L (75% of predicted).

Which of the following is the most appropriate therapy for this patient?
A. Albuterol by metered-dose inhaler as needed
B. Long-acting β-agonist plus as-needed albuterol
C. Long-acting β-agonist
D. Inhaled corticosteroids plus as-needed albuterol
E. Long-term antibiotic therapy

5. A 19-year-old woman is evaluated for possible asthma. She has known seasonal allergies that manifest as hay fever in fall and spring. Symptoms are restricted to her nose and eyes, and she has no history of wheezing or chest tightness. The patient had a methacholine test as part of a research study, which showed borderline response.

Which of the following would be the most appropriate management for this patient?
A. Inhaled corticosteroids and a long-acting β-agonist
B. Seasonal nasal corticosteroids and antihistamine
C. Albuterol inhaler as needed
D. Repeat methacholine challenge

6. A 37-year-old man with asthma is evaluated because he continues to have frequent attacks and now believes that his short-acting β-agonist is not providing relief. Other medications he reportedly uses include a long-acting β-agonist inhaler, inhaled high-dose corticosteroids, and a short-acting β-agonist inhaler as rescue medication. He has symptoms daily and nocturnal symptoms about twice per week.

On physical examination, he is in mild respiratory distress. Temperature is 37°C (98.6°F), blood pressure is 140/85 mm Hg, pulse rate is 90 beats/min, and respiration rate is 18 breaths/min. He has bilateral wheezing and oral thrush. Office spirometry shows FEV1 of 65% of predicted, which improves with bronchodilators to 85% of predicted. He has no history of recent viral upper respiratory infections, rhinitis, or symptoms of gastroesophageal reflux disease.

Which of the following is the best next step in this patient’s management?
A. Add a leukotriene inhibitor
B. Observe the patient using the metered-dose inhaler
C. Start oral prednisone therapy and have the patient return for a pill count
D. Have the patient return with a symptom and treatment log

Questions are largely from the ACP’s Medical Knowledge Self-Assessment Program (MKSAP). Go to www.annals.org/intheclinic/ to obtain up to 1.5 CME credits, to view explanations for correct answers, or to purchase the complete MKSAP program.