## In the Clinic

### Asthma

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diagnosis</td>
<td>ITC3-2</td>
</tr>
<tr>
<td>Treatment</td>
<td>ITC3-7</td>
</tr>
<tr>
<td>Practice Improvement</td>
<td>ITC3-13</td>
</tr>
<tr>
<td>Tool Kit</td>
<td>ITC3-14</td>
</tr>
<tr>
<td>Patient Information</td>
<td>ITC3-15</td>
</tr>
<tr>
<td>CME Questions</td>
<td>ITC3-16</td>
</tr>
</tbody>
</table>

The content of In the Clinic is drawn from the clinical information and education resources of the American College of Physicians (ACP), including ACP Smart Medicine 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 divisions and with the assistance of science writers and physician writers. Editorial consultants from ACP Smart Medicine and MKSAP provide expert review of the content. Readers who are interested in these primary resources for more detail can consult http://smartmedicine.acponline.org, http://www.acponline.org/products_services/mksap/15/?pr31, and other resources referenced in each issue of In the Clinic.

**CME Objective:** To review current evidence for diagnosis, treatment, and practice improvement of asthma.

The information contained herein should never be used as a substitute for clinical judgment.

© 2014 American College of Physicians
Asthma is a common respiratory illness characterized by airway hyper-responsiveness and inflammation. It affects over 300 million people globally (1), including 22 million adults in the United States alone. Although asthma mortality in the United States has declined, the morbidity and costs remain substantial. 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 effective therapies.

Diagnosis

What symptoms or elements of clinical history are helpful in diagnosing asthma?
Symptoms that should prompt clinicians to consider asthma are episodic wheezing, dyspnea, cough, difficulty taking a deep breath, and chest tightness (2, 3). A careful history to elicit the nature and timing of symptoms is paramount in diagnosing asthma. 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, occupational exposures, certain foods, and aspirin or non-steroidal anti-inflammatory drugs. Clinicians should also consider asthma in patients with chronic cough, especially if it is nocturnal, seasonal, or related to the workplace or a specific activity.

What physical examination findings are suggestive?
Because asthma is an episodic disease, the physical examination is less helpful than a carefully elicited history, unless a patient is having an active exacerbation. The clinician should listen for wheezing during tidal respirations or upon forced expiration, note the presence of a 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 their presence and absence (1, 3). The physical examination is sometimes most helpful in looking for evidence of alternative diagnoses. Inspiratory crackles may suggest interstitial lung disease or congestive heart failure. Abnormal heart sounds also might indicate heart failure or additional cardiac causes of dyspnea, such as valvular disease.

What are the indications for spirometry in a patient whose clinical presentation is consistent with asthma?
Several studies show a poor correlation among the presence, severity, and timing of wheezing and the degree of airflow obstruction (4, 5). Patients vary in degree of sensitivity to airflow limitations and can acclimate to the disability and thus become insensitive to airflow obstruction (6). Therefore, the National Heart, Lung, and Blood Institute (NHLBI) Expert Panel Report 3 recommends that all patients (adults and children > 5 years of age) in whom asthma is considered have objective assessments of pulmonary function (3). Specifically, initial pulmonary function testing should include spirometric measurement of the FEV₁, FVC, and the FEV₁/FVC ratio, before and 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, sex, and ethnicity (7). Post-
bronchodilator improvement ≥12% and 200 mL of the FEV₁ or FVC indicates significant reversibility and therefore increases the likeli-
hood of an asthma diagnosis (8). Spirometry should adhere to the standards of the American Tho-
racic Society (9). Of note, spirome-
try 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 FEV₁, may be an ac-
ceptable surrogate, with reduction in the FEV₁/FVC ratio signifying obstruction (10).

Does normal spirometry rule out a diagnosis of asthma? What additional testing should patients with normal spirometry have?

Abnormal spirometry (reversible obstruction) can confirm an asthma diagnosis, but normal spirometry does not rule out asthma. Because spirometry has limitations in sensi-
tivity and specificity, it is probably best used as part of a diagnostic strategy in conjunction with a com-
prehensive history, physical examination, and other laboratory data. Clinicians should consider further studies in patients with normal spirometry who have a clinical pic-
ture otherwise suggestive of asthma (Table 1).

Bronchoprovocation with metha-
choline 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. Alter-
natively, 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.

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

<table>
<thead>
<tr>
<th>Test</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulmonary function tests</td>
<td>Spirometry demonstrating reversible airflow obstruction supports the diagnosis of asthma but normal spirometry does not exclude it; lung volume and flow-volume loops should be evaluated to rule out other diagnoses</td>
</tr>
<tr>
<td>Bronchoprovocation</td>
<td>Positive results are diagnostic of airway hyperresponsiveness, which is a feature of, but may exist even in the absence of, asthma; negative results essentially rule out asthma</td>
</tr>
<tr>
<td>Chest radiograph</td>
<td>Useful in ruling out other diagnoses; a finding of hyperinflation is consistent with asthma but is often a transient phenomenon found in the setting of an acute exacerbation</td>
</tr>
<tr>
<td>Allergy testing</td>
<td>Skin or in vitro testing to determine sensitivity may be useful in patients with persistent disease to evaluate the role of allergens in asthma management; however, there is no clear diagnostic value</td>
</tr>
<tr>
<td>Complete blood count with differential</td>
<td>Mild eosinophilia is common in asthma; however, routine use has limited clinical utility</td>
</tr>
<tr>
<td>Sputum evaluation</td>
<td>Not indicated for routine initial evaluation; mild elevation is common with asthma; however, routine measurement is not recommended for initial evaluation</td>
</tr>
<tr>
<td>IgE</td>
<td>Utility not yet established; clinical trials under way</td>
</tr>
</tbody>
</table>

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 accept-
ed standardization (11). The test re-
quires sophisticated instrumentation and is labor-intensive and expensive. Although generally considered safe, it is generally not recommended in patients with an FEV₁ <65% of the predicted value (3). A low PC20 (the concentration of inhaled metha-
choline needed to induce a 20% de-
crease in the FEV₁) on methacholine challenge testing is diagnostic for airway hyperresponsiveness, a key feature of (though not limited to) asthma. Studies of methacholine challenge suggest that it is sensitive and has a high negative predictive value for the diagnosis of asthma (12-14). Although cold air has 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).

How should clinicians classify asthma?

Two reports, Expert Panel Report 3 by the National Asthma Education and Prevention Program, NHLBI, and National Institutes of Health, and Global Strategy for Asthma Management and Prevention by the Global Initiative for Asthma, have laid out specifics for assessing and managing asthma in children and adults. Both guidelines emphasize asthma control, defined as a patient having few or no symptoms, no activity limitations, few or no instances of need for rescue medication, normal lung function, and few exacerbations.

Patient assessment is split into 2 measures. Disease severity is defined as the intrinsic intensity of disease, which is assessed to initiate appropriate medication. Severity is most effectively assessed in patients not yet on long-term medication but can be estimated based on the lowest level of therapy needed to maintain control. Disease control is defined as the degree to which the manifestations of asthma are minimized and the goals of long-term control therapy are met. This measure is needed to maintain and adjust treatment as necessary. Responsiveness to treatment is generally defined as the ease with which asthma control is achieved by therapy, although precise parameters for

Table 2. Classification of Asthma Severity

<table>
<thead>
<tr>
<th>Components of Severity</th>
<th>Intermittent</th>
<th>Mild</th>
<th>Persistent</th>
<th>Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>Impairment*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Symptoms</td>
<td>≤2 d/wk</td>
<td>&gt;2 d/wk but not daily</td>
<td>Daily</td>
<td>Throughout the day</td>
</tr>
<tr>
<td>Nighttime awakenings</td>
<td>≤2 ×/mo</td>
<td>3–4 ×/mo</td>
<td>&gt;1 ×/d</td>
<td>Daily</td>
</tr>
<tr>
<td>SABA use for symptom control (not prevention of EIB)</td>
<td>≤2 d/wk</td>
<td>&gt;2 d/wk but not more than 1 ×/d</td>
<td>Some limitation</td>
<td>Extremely limited</td>
</tr>
<tr>
<td>Interference with normal activity</td>
<td>None</td>
<td>Normal FEV₁, between exacerbations; FEV₁ &gt;80% of predicted; FEV₁/FVC normal</td>
<td>Minor limitation</td>
<td>FEV₁ &lt;60% of predicted; FEV₁/FVC reduced 5%</td>
</tr>
<tr>
<td>Lung function</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exacerbations</td>
<td>0–1/y</td>
<td>≥2/y</td>
<td>≥2/y</td>
<td>≥2/y</td>
</tr>
<tr>
<td>Risk</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recommended step for initiating treatment (see Figure for treatment steps)*</td>
<td>Step 1</td>
<td>Step 2</td>
<td>Step 3; consider short courses of systemic corticosteroids</td>
<td>Step 4 or 5; consider short courses of systemic corticosteroids</td>
</tr>
</tbody>
</table>

Adapted from reference 3. EIB = exercise-induced bronchospasm; SABA = short-acting β₂-agonist.

*Normal FEV₁/FVC ratio: 8–19 years old, 85%; 20–39 years old, 80%; 40–59 years old, 75%; 60–80 years old, 70%.

*Frequency and severity may fluctuate over time for patients in any severity category. Relative annual risk for exacerbations may be related to FEV₁.

*Level of severity is determined by assessment of both impairment and risk. Assess impairment domain by patient’s/caregiver’s recall of previous 2–4 wk and spirometry. Assign severity to the most severe category in which any feature occurs.

*In 2–6 weeks, evaluate the level of asthma control that is achieved and adjust therapy accordingly. Therapy should be initiated based on the severity of impairment at the time of initiation of therapy: step 1 for intermittent impairment, step 2 for mild persistent impairment, step 3 for moderate persistent impairment, and step 4 or 5 for severe persistent impairment.
responsiveness measurement have not been determined.

Asthma severity (Table 2) and control (Table 3) are classified according to two domains: impairment and risk. This change was made to emphasize the need to consider both domains in asthma management. Each category of impairment is defined by the frequency of symptoms, nocturnal symptoms, rescue inhaler use, interference with normal activity, and spirometric measurements. Each category of risk is defined by the frequency of exacerbations. The NHLBI Expert Panel 3 Report suggests obtaining spirometry at the following intervals to aid in the classification of asthma: at the time of initial diagnosis and evaluation; after stabilization of symptoms with therapy; after any prolonged exacerbations or progressive, chronic worsening, and every 1–2 years for routine monitoring of disease progression (3).

**What comorbid conditions and alternative diagnoses should clinicians consider in patients with suspected asthma?**

The differential diagnosis of asthma is broad (Table 4). Clinicians should consider one of these alternative diagnoses when asthma is difficult to control or if the patient has atypical signs and symptoms.
Table 4. Differential Diagnosis of Asthma

<table>
<thead>
<tr>
<th>Condition</th>
<th>Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>COPD</td>
<td>Airway destruction less reversible; typically seen in older patients with a history of smoking</td>
</tr>
<tr>
<td>Vocal cord dysfunction</td>
<td>Abrupt onset and end of symptoms; monophonic wheeze; more common in younger patients; confirm with laryngoscopy and/or flow-volume loop</td>
</tr>
<tr>
<td>Heart failure</td>
<td>Dyspnea and often wheezing; crackles on auscultation; limited response to asthma therapy; cardiomegaly; edema; elevated BNP; other features of heart failure</td>
</tr>
<tr>
<td>Bronchiectasis</td>
<td>Cough productive of large amounts of purulent sputum; rhonchi and crackles are common; may have wheezing and clubbing; confirmed by CT imaging</td>
</tr>
<tr>
<td>Allergic bronchopulmonary aspergillosis</td>
<td>Recurrent infiltrates on chest radiograph; eosinophilia; high IgE levels; frequent need for corticosteroid treatment</td>
</tr>
<tr>
<td>Cystic fibrosis</td>
<td>Cough productive of large amounts of purulent sputum; rhonchi and crackles are common; prominent clubbing; may have wheezing</td>
</tr>
<tr>
<td>Mechanical obstruction</td>
<td>More localized wheezing; if central in location, flow-volume loop may provide a clue</td>
</tr>
</tbody>
</table>

BNP = B-type natriuretic peptide; COPD = chronic obstructive pulmonary disease; CT = computed tomography.


particularly if spirometry is inconsistent with or nondiagnostic of asthma. Further testing, such as complete pulmonary function testing that includes lung volumes and diffusing capacity, may be revealing. For example, evidence of a lack of reversibility of airflow obstruction suggests chronic obstructive pulmonary disease (COPD), or restrictive patterns with diminutions in the FEV1 and FVC but a normal FEV1/FVC ratio suggests interstitial lung disease. These conditions can also coexist in a patient who has asthma and referral to a specialist may be indicated in these situations (see next section). An important difference between asthma and COPD is the history of smoking. Although 30% of patients with asthma in the United States smoke, COPD often occurs in older persons with a substantial history of cigarette smoking and is manifest by chronic bronchitis and emphysema. Patients with COPD may demonstrate reversibility with bronchodilators on pulmonary function testing, but it is less common, can vary between and within patients, can change over time, and can differ according to the bronchodilator used (16). Inspection of the flow-volume loop may reveal evidence of a fixed or variable airway obstruction or, together with direct visualization of the larynx during acute symptoms, may be useful in indentifying vocal cord paralysis. A plain chest radiograph 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. Chronic cough, dyspnea, or recurrent wheezing, although each consistent with asthma, may be due to other disorders including COPD, vocal cord dysfunction, cystic fibrosis, obstructive sleep apnea, the Churg-Strauss syndrome, allergic bronchopulmonary aspergillosis, interstitial lung disease, bronchiectasis, congestive heart failure, and pulmonary hypertension, or may be side effects of medications. Evidence shows that difficult-to-control asthma may be a result of comorbid conditions and that standardized evaluation of patients for comorbidity was associated with improved asthma control (17).

When should primary care clinicians consider referring patients with suspected asthma to specialists for diagnosis?

Consultation with a pulmonologist should be considered before ordering provocative pulmonary function testing because testing is time- and labor-intensive and requires skilled performance and interpretation. Patients presenting with atypical symptoms, who have abnormal chest radiographs, pulmonary function tests suggesting both obstruction and restriction, unusual manifestations of the disease, or who display suboptimal response to therapy may benefit from referral to a pulmonologist. Referral to an allergist may be helpful for patients with asthma that seems to have an allergic component, such as seasonal variation in asthma severity or sensitivity to specific environmental exposures.
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 the Box: Measures to Reduce Dust Mite and Other Environmental Allergen and Irritant Exposure). 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, even modest remediation can be beneficial.

The NHLBI Expert Panel Report 3 recognized environmental smoke exposure as a common cause of asthma exacerbations (3), and several studies have impugned active and passive cigarette smoking as a cause of decreasing lung function in adult asthma (18, 19). One study demonstrated that elevated levels of biomarkers of tobacco exposure were associated with increased asthma severity (20). Another 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]) (21).

What evidence supports the use of indoor air-cleaning devices for patients with asthma?
Given the recognition that environment plays a critical role in airway hygiene, it may seem logical that indoor air-cleaning devices are beneficial. However, there is little evidence to suggest that HEPA filters or air duct cleaning control asthma, and they are not currently recommended as part of a multifaceted plan to reduce allergen exposure. Humidifiers may actually increase allergen levels and must be cleaned often. A multidisciplinary committee convened by the Institute of Medicine reviewed available evidence concerning the impact of ventilation and air cleaning on asthma (22). Although it concluded that particle air cleaning may reduce symptoms in certain situations, evidence is inadequate to broadly recommend air cleaning for patients with asthma. Keeping household humidity below 50% with dehumidifiers or air conditioners reduces dust mites and mold and is recommended by the Expert Panel Report 3 (3).

How should clinicians select from among available drug therapy for asthma?
The Appendix Table (available at www.annals.org) summarizes drugs...
available to treat asthma. The goals of asthma therapy are to achieve asthma control by the following means: reduce impairment through reduction of chronic and troublesome symptoms; minimize rescue bronchodilator use; maintain normal (or near normal) spirometry; minimize interference with activities; and meet patient’s satisfaction with care and to reduce risk by the following means: prevent exacerbations; prevent loss of lung function; and provide optimal pharmacotherapy with minimal adverse effects.

The Figure presents a stepwise approach to pharmacotherapy. Stepwise therapy consists of agents for acute relief of symptoms (rescue therapy) and for long-term control. Rescue therapy is critical for all patients regardless of asthma severity. Even patients with intermittent asthma can have severe exacerbations. Patients with persistent symptoms require a long-term controller in addition to rescue therapy. Therapy should be initiated based on the severity of impairment at the time of initiation of therapy: step 1 for intermittent impairment, step 2 for mild persistent impairment, step 3 for moderate persistent impairment, and step 4 or 5 for severe persistent impairment. Impairment status is determined by the most impaired variable (e.g., worst of symptoms, nighttime awakenings).

After initiation of therapy, the regimen should be adjusted based on

**Figure.** Stepwise approach for managing asthma in adults. EIB = exercise-induced bronchospasm; ICS = inhaled corticosteroids; LABA = long-acting β-agonists; LTRA = leukotriene-receptor agonists; SABA = short-acting β-agonists.
the level of asthma control (Table 3 and Figure). If asthma is not well-controlled, stepping up to more intense therapy is indicated. A step up in treatment may involve any or all of the following: an increase in the inhaled corticosteroid (ICS) dose, addition of a second controller, and a brief course of oral steroids to achieve control more rapidly. If symptoms are well-controlled on a given regimen for 3 months or more, stepping down to less intensive therapy is indicated. A step down in treatment may involve stopping the second controller (such as a long-acting β₂-agonist [LABA] bronchodilator) or reducing the dose of ICS. A decrease in ICS dose by 25%–50% over time is an appropriate initial target. It is important that the patient have instructions to call immediately if symptoms start to increase.

Clinicians should review therapy 2–6 weeks after initiation of or stepping up/down therapy and then every 1–6 months. The frequency of follow-up should depend on level of control. 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 intermittent asthma may only need a quick-relief medication (short-acting β-agonists [SABAs]) on an as-needed basis. SABAs are the drugs of choice for reversal of acute bronchospasm and are safe and well-tolerated. Patients with persistent asthma (mild, moderate, or severe) maintained on long-term controller therapy should also receive a SABA 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 require long-term controller therapy.

Patients with mild persistent asthma should receive a long-term controller medication, usually a low-dose ICS. Compared with patients with intermittent asthma, patients with mild persistent asthma are more prone to underlying inflammation and disease exacerbations. Low-dose ICSs have been shown to reduce risk for exacerbations, bronchial hyperresponsiveness, and need for rescue β-agonist use and to control symptoms. Alternatives to ICSs are leukotriene-receptor antagonist medications (e.g., montelukast, zafirlukast) or cromolyn. Of note, LABA monotherapy is not recommended for long-term control of asthma because studies suggest a risk for increased morbidity and mortality in some patients (23).

The therapy of choice in patients with moderate persistent asthma is either low-dose ICSs and a LABA or a moderate dose of a single long-term controller medication (excluding LABAs as outlined above). Evidence suggests that patients who remain symptomatic while taking moderate doses of ICSs benefit from the addition of a long-acting bronchodilator, such as 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 ICS alone (24–26). 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 unclear whether controlling the disease with high-dose ICSs or moderate-dose ICs 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 ICSs, a dry-powder inhaler containing salmeterol and fluticasone was more effective in improving...
LABAs may help improve asthma symptoms, but as mentioned above, they may also increase risks for adverse outcomes. Therefore, patients started on these medications should be followed closely. A meta-analysis of 19 randomized clinical trials found that, compared with placebo, LABAs 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%) (23). 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 ICSs seemed to be at highest risk for these outcomes. Guidelines suggest that adding a LABA to low-dose ICS and increasing the dose of ICS (step 3, see Figure) are equally preferred options. This balances the established beneficial effects of combination therapy in older children and adults and the potential increased risk for severe exacerbations reported with daily use of LABA.

Patients with severe persistent asthma may require three 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 ICSs to leukotriene receptor modifiers (such as montelukast) revealed that the ICSs were more effective. The addition of montelukast to the regimen of a patient requiring high-dose ICSs, however, allowed a significant reduction in the dose of the ICS while maintaining asthma control (28).

In a randomized clinical trial of patients with inadequate symptom control despite low- to moderate-dose ICS, the addition of montelukast improved FEV1, daytime symptoms, and nocturnal awakenings (29). A systematic review of trials comparing the addition of daily leukotriene-receptor antagonists or LABAs to ICSs in patients with severe asthma concluded that LABAs were better than leukotriene antagonists in preventing the need for rescue therapy and systemic steroids and improved lung function and symptoms (30).

Until recently, anticholinergic agents were not a part of the chronic medication regimen for asthma. However, recent studies have suggested that there may be a role for long-acting anticholinergic agents in chronic asthma therapy.

In one randomized trial of symptomatic patients with an FEV1 <80% predicted and a history of at least one exacerbation in the prior year, addition of tiotropium to a regimen of inhaled glucocorticoid and LABA was associated with a longer time until another exacerbation and a modest improvement in FEV1, compared with placebo (31). As such, tiotropium can be considered in patients who remain poorly controlled despite two agents.

Omalizumab is a monoclonal antibody that binds to IgE and has been shown to reduce exacerbations in patients with severe persistent asthma despite therapy with high–dose ICSs and LABA therapy and often additional pharmacologic therapies (32). 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. Additional biological therapies, such as a monoclonal antibody to the interleukin-4 receptor, are under investigation for the treatment of asthma (33).

What is the role of nonpharmacologic therapy? Many patients are interested in nonpharmacologic therapy for asthma, such as acupuncture, and

complementary or herbal therapies. The Expert Panel Report 3 advises that there is inadequate evidence to either support or refute the role of such therapies in chronic asthma management in general, with the exception that the panel specifically recommends against acupuncture. Physicians are also advised to counsel patients on the possible risks of complementary therapy, such as herbal medications, as regulation and formulations of these may not be standardized.

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

In some patients, exercise induces bronchospasm. Symptoms often occur with vigorous exercise in cold, dry air. The Expert Panel Report 3 recommends that patients should not have to limit desired activity because of exercise-induced bronchospasm. Patients who have normal baseline pulmonary function but experience exercise-induced symptoms, such as cough, shortness of breath, or wheezing, can be treated effectively with albuterol, cromolyn sodium, or nedocromil 15–30 minutes before exercise. If exercise-induced symptoms persist, addition of long-acting bronchodilators or leukotriene antagonists may be helpful. Recent evidence, however, suggesting that monotherapy with long-acting bronchodilators may cause adverse outcomes in asthma cautions against using these agents as monotherapy in exercise-induced asthma (23, 34). Despite these concerns, evidence 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 bronchospasm in the context of the patient’s overall therapy.

Many patients who present with putative exercise-induced bronchospasm may have abnormal pulmonary function test results at baseline. Such patients should be treated according to the regimen described by the Expert Panel Report 3 (3).

**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 specific clinical situations (see the Box: Clinical Scenarios That Should Prompt Specialist Referral).

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 a patient who has asthma with an atopic component may benefit from referral to an allergist.

**When should oral corticosteroids be used for outpatient treatment?**

Selected patients who have an acute increase in asthma symptoms may be managed as outpatients, with appropriate escalation of therapy and instructions to seek urgent care rapidly if symptoms persist or worsen. Oral corticosteroids should be given to patients who have symptoms that are incompletely controlled after 2 doses within 20 minutes of 2 to 6 puffs of SABAs (i.e., wheezing or dyspnea persists). Patients who are started on oral corticosteroids as an outpatient should continue frequent short-acting β-agonists (every 4 hours) and follow-up within 1 day with a physician to ensure improved control. They

---

**Clinical Scenarios That Should Prompt Specialist Referral**

**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**

**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**

---


should also be instructed to immediately seek medical attention if symptoms persist or worsen or if SABAs are required more frequently than every 4 hours.

**How should the patient be educated to respond when symptoms increase?**

The Expert Panel Report 3 emphasizes the importance of patient education and involvement in self-management of asthma, including acute exacerbations (3). Patients should know the early signs and symptoms of deterioration and the appropriate action to take in response, as early intervention may prevent emergency department visits and hospitalization. Physicians and patients should agree on a written action plan, which should include daily management, how to recognize signs and symptoms of worsening, and how to adjust medications in response to acute symptoms or changes in the peak expiratory flow rate (PEFR). The plan should specifically address how patients should adjust medications and doses and when they should seek medical attention. Patients with moderate or severe disease should have medications (such as oral corticosteroids) and equipment (such as a nebulizer machine) available at home for immediate treatment of exacerbations.

**When is hospitalization indicated?**

Patients who have a sustained response to treatment in outpatient settings generally 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 account for patient characteristics (including factors listed in the Box: Factors Associated With Poor Outcomes of Asthma Exacerbations), severity of disease, and initial response to short-term therapy. Additional variables to consider include the availability of assistance to the patient in case of need and the reliability of close follow-up care. Patients with a moderate or severe exacerbation and an incomplete response to therapy may need hospitalization. A moderate exacerbation is defined as one where the FEV1 is 40%–69% predicted or the PEFR is 40%–69% of personal best, or the symptoms and physical examination findings are moderate (such as persistent wheezing but ability to speak in full sentences). An exacerbation is severe if the FEV1 or PEFR ratio <40%; when symptoms are severe; or when physical examination findings include signs of severe respiratory distress, such as muscle retraction, use of accessory muscles, inability to speak in full sentences, or confusion or lethargy. When posttreatment PEFR remains <40% 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).*

**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 the Box: Factors Associated With Poor Outcomes of Asthma Exacerbations).
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, 2–4 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 Expert Panel Report 3 suggests routine follow-up every 1–6 months (3); 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 (39, 40).

Treatment... Patients should try to understand and 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 SABAs available for relief of acute symptoms. For patients with persistent asthma, treatment with long-term controller medications can be stepped up or down as needed to maintain disease control. The key to a successful step-up/step-down treatment plan is to closely monitor symptoms. Serial measures of asthma control should guide treatment changes to minimize the potential risk for asthma exacerbations and long-term side effects. An acute increase in symptoms requires prompt recognition and increase in treatment, and all patients should be instructed on how to recognize the early signs of clinical deterioration and how to respond. Careful evaluation and monitoring are required to identify when patients with an acute increase in symptoms require hospitalization.

Do U.S. stakeholders consider asthma care when evaluating the quality of care a physician delivers?

In April 2005, the Ambulatory Care Quality Alliance 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), two of which focus on asthma care. The National Quality Forum has defined and/or endorsed physician-specific similar measures of quality of asthma care (see the Box: Physician Quality Measures for Asthma Care Endorsed by the National Quality Forum). As part of the Affordable Care Act, beginning in 2015, physician reimbursement from Centers for Medicare & Medicaid Services (CMS) will be subject to value-based modification, based on some of the measures described.

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

Physician Quality Measures for Asthma Care Endorsed by the National Quality Forum

Assessment of asthma control: the percentage of patients aged 5 to 40 years with a diagnosis of asthma who were evaluated during at least one office visit during the measurement year for frequency of daytime and nocturnal asthma symptoms.

Assessment of appropriate therapy: the percentage of patients 5 to 64 years of age during the measurement year who were identified as having persistent asthma and who were appropriately prescribed medication during the measurement year.

In the Clinic

Tool Kit

Asthma
ACP Smart Medicine Module

http://smartmedicine.acponline.org/content.aspx?gboId=108%8&result
Click=3&ClientActionType=80LR%20Direct%20to%20Content
&ClientActionData=Module%20link%20Click

Access the American College of Physicians (ACP) Smart Medicine module on asthma.

Patient Information
www.nlm.nih.gov/medlineplus/asthma.html

Information on asthma from the National Institutes of Health MedlinePlus, including an interactive tutorial in English and Spanish.

www.nhlbi.nih.gov/health/health-topics/topics/asthma/
www.nhlbi.nih.gov/health-spanish/health-topics/temas/asthma/

Information for patients on asthma, in English and in Spanish, from the National Heart, Lung, and Blood Institute (NHLBI).

www.cdc.gov/asthma/faqs.htm

Answers to frequently asked questions about asthma from the Centers for Disease Control and Prevention.

Clinical Guidelines
www.nhlbi.nih.gov/guidelines/asthma/asthsumm.pdf

Evidence-based guidelines for the diagnosis and management of asthma from the National Asthma Education and Prevention Program in 2007.


Practice parameter on the pathogenesis, prevalence, diagnosis, and management of exercise-induced bronchoconstriction from the American Academy of Allergy, Asthma and Immunology; the American College of Allergy, Asthma and Immunology; and the Joint Council of Allergy, Asthma and Immunology in 2010.


Diagnostic Tests and Criteria
http://smartmedicine.acponline.org/content.aspx?gboId=108%8&result
Click=3&ClientActionType=80LR%20Direct%20to%20Content
&ClientActionData=Module%20link%20Click

List of laboratory and other studies for diagnosis and risk stratification of patients with asthma from ACP Smart Medicine.

Quality-of-Care Guidelines
www.aaaai.org/Aaaai/media/MediaLibrary/PDF%20Documents/Practice%20and%20Parameters/attaining-optimal-asthma-control.pdf

Practice parameter on attaining optimal asthma control from the American Academy of Allergy, Asthma and Immunology and the American College of Allergy, Asthma and Immunology in 2005.

www.cdc.gov/mmwr/preview/mmwrhtml/rr5206a1.htm

Key clinical activities for quality asthma care from the National Asthma Education and Prevention Program in 2003.


Asthma performance measures from the Ambulatory Care Quality Alliance address asthma.
WHAT YOU SHOULD KNOW ABOUT ASTHMA

What is asthma?
- A long-term disease that affects the lungs and causes wheezing, chest tightness, difficulty breathing, and coughing.
- When an asthma attack occurs, tubes (bronchi) that bring air to the lungs tighten, and breathing becomes difficult.
- An asthma attack can occur when something irritates your lungs, such as smoke, mold, or dust mites.

How is it diagnosed?
- Your doctor will ask you questions about your symptoms and whether anyone in your family has had asthma or other breathing problems.
- A simple breathing test called spirometry may be performed to check how well your lungs are functioning.
- Spirometry measures how much air you can breathe out after taking a very deep breath.

How is it treated?
- Long-term medicines that you take every day can help prevent asthma attacks, but don’t help you during an attack.
- Quick-relief medicines can reduce your symptoms when attacks occur.
- If you need to use your quick-relief medicines more and more, your doctor may need to prescribe a different medicine.
- A personalized asthma action plan helps guide you on when to take medications and how to adjust them to keep your asthma under control.
- Call your doctor or go to the hospital if it is hard to breathe and your medicines are not helping.

How can you prevent an asthma attack?
- Stay away from what makes your asthma worse, such as dust, smoke, animals, and cold or dry air.
- Don’t smoke, and stay away from people who do.
- Asthma-proof your home—for example, discard old carpets and drapes, and use a special mattress and pillow covers.
- Use air conditioners and dehumidifiers.
- Take your medicines that prevent attacks every day, even when you don’t have symptoms.
- Take your medicines that stop attacks when you need them.
- Learn the right way to use your inhalers.

For More Information

www.nhlbi.nih.gov/health/public/lung/asthma/have_asthma.htm
A handout titled, “So You Have Asthma: A Guide for Patients and Their Families” and asthma facts from the NHLBI.

www.nhlbi.nih.gov/health/public/lung/asthma/actionplan_text.htm
An asthma action plan worksheet from the NHLBI.

www.nlm.nih.gov/medlineplus/ency/presentations/100200_1.htm
A tutorial on proper use of a metered-dose inhaler.
CME Questions

1. A 50-year-old woman is evaluated for a recent increase in asthma symptoms characterized by daily cough and dyspnea. She reports waking up two to three nights per week with asthma symptoms. She has no postnasal drip, nasal discharge, fever, or heartburn. Her current medications are medium-dose inhaled corticosteroids and albuterol as needed. She is able to demonstrate proper use of her metered-dose inhalers. On physical examination, she appears comfortable and is in no respiratory distress. Pulse rate is 76/min, and respiration rate is 18/min. Pulmonary examination reveals bilateral wheezing. The remainder of the examination is normal.

Which of the following is the most appropriate next step in management?
A. Add a long-acting β₂-agonist inhaler
B. Add an ipratropium metered-dose inhaler
C. Double the dose of inhaled corticosteroids
D. Start a 10-day course of a macrolide antibiotic

2. A 51-year-old man is evaluated for worsening of asthma symptoms characterized by frequent daytime wheezing and cough, as well as nocturnal awakening related to asthma two to three times per week. He has been using his inhalers regularly without adequate relief. He has not had recent upper respiratory tract infection, sinusitis, postnasal drip, or new exposures. He is taking an inhaled corticosteroid and inhaled albuterol.

On physical examination, temperature is 37.0°C (98.6°F), blood pressure is 135/80 mm Hg, pulse rate is 80/min, and respiration rate is 18/min. Pulmonary examination reveals bilateral wheezing. Spirometry shows an FEV₁ of 90% of predicted and an FEV₁/FVC ratio of 80%. Following an inhaled bronchodilator, FEV₁ improves to 90% of predicted.

Which of the following is the most appropriate next step in management?
A. Add a leukotriene receptor antagonist
B. Add prednisone
C. Observe the patient using his inhalers
D. Record symptoms and medication use over 2 weeks

3. A 32-year-old man is evaluated for chronic cough that has lasted nearly 1 year. He recalls noticing the cough initially after a "bad cold." At that time he received two courses of antibiotics (including a macrolide and a fluoroquinolone) with improvement in the acute symptoms. However, he subsequently noted persistent cough, particularly at nighttime and on cold days. Episodes of cough often occur after exercise or laughing. He is currently asymptomatic, with no postnasal drip, nasal congestion, or heartburn. He does not smoke. He has no history of occupational or other exposures. He has a remote history of hay fever. Multiple family members have seasonal allergies. His only medication is a proton pump inhibitor, which he has taken for the past 6 months without benefit.

On physical examination, vital signs are normal. The oropharynx appears normal, with no cobblestone appearance. There is no mucus in the nostrils or oropharynx. Pulmonary examination is normal. Spirometry shows an FEV₁ of 90% of predicted and an FEV₁/FVC ratio of 80%. Chest radiograph is normal.

Which of the following is the most appropriate diagnostic test to perform next?
A. Bordetella-specific antibodies
B. Bronchial challenge
C. Bronchoscopy
D. Chest CT scan

4. A 20-year-old man is evaluated during a routine examination. He has a history of episodes of bronchitis since early childhood; symptoms include productive cough, wheezing, and shortness of breath. He is being treated for asthma, but his symptoms have not been well-controlled. His current medications are a medium-dose inhaled corticosteroid and a long-acting β₂-agonist, with documented satisfactory inhaler technique.

On physical examination, temperature is 37.2°C (99.0°F), blood pressure is 110/65 mm Hg, pulse rate is 82/min, and respiration rate is 18/min; BMI is 20 kg/m². Small nasal polyps are noted. Pulmonary examination reveals diffuse rhonchi and scattered wheezing. The neck veins are flat. Cardiac examination reveals a normal S₁ and S₂ with a soft 1/6 systolic murmur. Clubbing is noted. There is no pedal edema, and pulses are intact and symmetric. Oxygen saturation breathing ambient air is 93%.

Laboratory studies reveal a hemoglobin level of 11 g/dL (110 g/L) and a leukocyte count of 9800/µL (9.8 × 10⁹/L). Chest radiograph shows increased bronchial markings consistent with bronchiectasis in the upper lung zones.

Which of the following is the most appropriate next step in management?
A. Measure sweat chloride
B. Perform bronchoscopy
C. Perform echocardiography
D. Record symptoms and medication use over 2 weeks

Questions are largely from the ACP’s Medical Knowledge Self-Assessment Program (MKSAP, accessed at http://www.acponline.org/products_services/mksap/15/?pr31). Go to www.annals.org/intheclinic/ to complete the quiz and earn up to 1.5 CME credits, or to purchase the complete MKSAP program.
<table>
<thead>
<tr>
<th>Drug or Drug Class</th>
<th>Dosing</th>
<th>Side Effects</th>
<th>Precautions</th>
<th>Clinical Use</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Inhaled short-acting (\beta_2)-agonists</strong></td>
<td></td>
<td></td>
<td>Caution with: CV disease, hyperthyroidism, diabetes, narrow-angle glaucoma, seizure disorder</td>
<td>First line for mild, intermittent symptoms</td>
</tr>
<tr>
<td>Albuterol (Proventil HFA, Ventolin HFA, Proair HFA, Accuneb)</td>
<td>MDI (90 µg/inhalation): 2 inhalations every 4–6 h prn. Nebulizer: 2.5 mg every 6–8 h pm. For acute exacerbations, MDI can increase to 4–8 puffs every 1–4 h, or nebulizer to 2.5–10 mg every 1–4 h</td>
<td>Sympathomimetic effects, such as tremor and tachycardia. Hypokalemia, hyperglycemia, hypersensitivity reactions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Levalbuterol (Xopenex, Xopenex HFA)</td>
<td>MDI (45 µg/inhalation): 2 inhalations every 4–6 h pm. Nebulizer: 0.63–1.25 mg every 8 h. For acute exacerbations, MDI can increase to 4–8 inhalations every 1–4 h, or nebulizer to 1.25–5 mg every 1–4 h</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pirbuterol (Maxair)</td>
<td>MDI (200 µg/inhalation): 2 inhalations every 4–6 h pm. For acute exacerbations, can increase to 4–8 inhalations every 1–4 h</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Inhaled corticosteroids</strong></td>
<td>Dose depends on previous asthma therapy</td>
<td></td>
<td>Caution with diabetes</td>
<td>For mild-severe persistent asthma</td>
</tr>
<tr>
<td>Beclomethasone (QVAR) Inhaler</td>
<td>Inhaler (40, 80 µg/inhalation): 40–160 µg 2 times/d</td>
<td>Xerostomia, flushing, catarracts, glaucoma, oral canthi, hoarseness, purpura. Low incidence of: HPA suppression, bone loss</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Budesonide (Pulmicort, Flexhaler Pulmicort Turbuhaler)</td>
<td>DPI (90, 180 µg/inhalation): 360 µg 2 times/d. DPI (200 µg/inhalation): 200–400 µg 2 times/d</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ciclesonide (Alvesco)</td>
<td>MDI (80, 160 µg/inhalation): 80–320 µg 2 times/d</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Flunisolide (Aerospan HFA)</td>
<td>Inhaler (80 µg/inhalation): 160 µg 2 times/d</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fluticasone (Flovent HFA, Flovent Diskus)</td>
<td>MDI (44, 110, 220 µg/inhalation): 88–440 µg 2 times/d. DPI (50, 100, 250 µg/inhalation): 100–1000 µg 2 times/d</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mometasone (Asmanex Twisthaler)</td>
<td>DPI (110, 220 µg/inhalation): 220 µg once daily in the PM. Maximum 220–440 µg 2 times/d</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Triamcinolone (Azmacort)</td>
<td>MDI (75 µg/inhalation): 150 µg 3–4 times/d or 300 µg 2 times/d. Maximum 1200 µg total daily dose</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leukotriene modifiers</td>
<td></td>
<td>Rare neuropsychiatric events</td>
<td></td>
<td>Alternatives for mild-moderate persistent asthma</td>
</tr>
<tr>
<td>Montelukast (Singulair)</td>
<td>10 mg once daily in the PM</td>
<td>Rare systemic eosinophilia</td>
<td>Avoid with hepatic disease. Inhibits CYFs 1A2, 2C8, 2C9 and 3A4. Increased INR with warfarin</td>
<td></td>
</tr>
<tr>
<td>Zafirlukast (Accolate)</td>
<td>20 mg 2 times/d</td>
<td>Elevated hepatic enzymes, hypersensitivity reactions, rare systemic eosinophilia</td>
<td>Avoid with hepatic disease. Check LFTs at baseline and periodically. Substrate and potent inhibitor of CYP1A2</td>
<td></td>
</tr>
<tr>
<td>Zileuton (Zyflo CR)</td>
<td>Extended-release: 1200 mg 2 times/d, within 1 h after meals</td>
<td>Elevated hepatic enzymes, flu-like syndrome</td>
<td>Avoid with hepatic disease.</td>
<td></td>
</tr>
</tbody>
</table>
### Respiratory anti-inflammatory agent

**Cromolyn (Intal)**
- MDI (800 µg/spray): 2 sprays 4 times/d.
- Nebulizer: 20 mg 4 times/d

**Inhaled long-acting β₂-agonists**
- **Formoterol (Foradil Aerolizer)**
- Powder in capsules for use with Aerolizer: 12 µg every 12 h
- **Salmeterol (Serevent Diskus)**
- 50 µg (1 oral inhalation) every 12 h

**Oral corticosteroids**
- **Prednisone**
  - 40-80 mg total daily dose, dosed 1-2 times/d, for a total course of 3-10 days; tapered doses may be considered
- **Prednisolone (Prelone, Flo-Pred, Orapred)**
  - 40-80 mg total daily dose, dosed 1-2 times/d, for a total course of 3-10 days; tapered doses may be considered
- **Methylprednisolone PO or IV**
  - 40-80 mg total daily dose, dosed 1-2 times/d, for a total course of 3-10 days; tapered doses may be considered

**Methylxanthine**
- **Theophylline (Theolar, Theo-24)**
  - Dose must be individualized.
  - Aim for serum levels between 5 and 15 µg/mL. IV: 0.2-0.4 mg/kg/h Immediate-release: Initially 300 mg total daily dose, dosed every 6-8 h. Can increase to 400-1600 mg total daily dose, dosed every 6-8 h. Extended-release: Initially 300 mg total daily dose, dosed every 8-12 h. Can increase to 400-1600 mg total daily dose, dosed every 8-12 h. Controlled-release (Theo-24): Initially 300-400 mg every 24 h. Can increase to 400-1600 mg total daily dose, dosed every 12-24 h
- **Ipratropium (Atrovent, Atrovent HFA)**
  - MDI (17 µg/inhalation): 2-3 inhalations 4 times/d. Nebulizer: 500 µg 3-4 times/d
- **Tiotropium (Spiriva)**
  - Powder in capsules for use with HandiHaler: 18 µg once daily

**Anti-IgE antibody**
- **Omalizumab (Xolair)**
  - 150-375 mg SC every 2 or 4 weeks. Dose based on baseline serum IgE and body weight
  - CV and cerebrovascular adverse events, infection, rare systemic eosinophilia

### Adverse Effects

**Respiratory anti-inflammatory agent**
- Bronchospasm, throat irritation, cough, severe anaphylaxis

**Inhaled long-acting β₂-agonists**
- Sympathomimetic effects, such as tremor and tachycardia. Paradoxical bronchoconstriction, hypersensitivity reactions. Rare: hypokalemia, hyperglycemia

**Oral corticosteroids**
- Long-term use can result in: HPA suppression, immunosuppression, hypertension, adverse neurologic effects, glucose intolerance, weight gain, myopathy, cataracts, osteoporosis

**Methylxanthine**
- GI side effects, CV adverse effects

**Inhaled anticholinergics**
- Dry mouth, additional anti-cholinergic effects

**Anti-IgE antibody**
- CV and cerebrovascular adverse events, infection, rare systemic eosinophilia

### Contraindications and Warnings

**Respiratory anti-inflammatory agent**
- Alternative for mild persistent asthma

**Inhaled long-acting β₂-agonists**
- Black box warning: Asthma-related death. Caution with: CV disease, hyperthyroidism, diabetes, narrow-angle glaucoma, seizure disorder. Tolerance can occur over time

**Oral corticosteroids**
- For moderate-severe persistent asthma. Must also use an asthma controller

**Methylxanthine**
- Narrow therapeutic index. Many drug interactions due to CYP450 hepatic metabolism. Use low dose with: hepatic disease, HF, elderly. Caution with: cardiac disease, thyroid disease, peptic ulcer disease, prostatic hypertrophy, seizure disorder, smoking

**Inhaled anticholinergics**
- Caution with: closed-angle glaucoma, bladder neck obstruction, prostatic hypertrophy

**Anti-IgE antibody**
- Black box warning: Anaphylaxis. Caution in patients with high risk for malignancy, For severe persistent asthma not controlled
<table>
<thead>
<tr>
<th>Magnesium sulfate</th>
<th>2 g IV</th>
<th>caution with live virus vaccines</th>
<th>Avoid with AV block. Caution with CKD</th>
</tr>
</thead>
</table>

**Combination agent:**

**Corticosteroid/long-acting β₂-agonist**

- **Budesonide/Formoterol** (Symbicort): 80/4.5 µg, 160/4.5 µg; dosed 2 inhalations 2 times/d
- **Mometasone/Formoterol** (Dulera): 100/5 µg, 200/5 µg; dosed 2 inhalations 2 times/d
- **Fluticasone/Salmeterol** (Advair Diskus, Advair HFA)
  - DPI: 100/50 µg, 250/50 µg, 500/50 µg; dosed 1 inhalation 2 times/d. MDI: 45/21 µg, 115/21 µg, 230/21 µg; dosed 2 inhalations 2 times/d

* = first-line agent; CKD = chronic kidney disease; CNS = central nervous system; CrCl = creatinine clearance; CV = cardiovascular; CYP = cytochrome P450 isoenzymes; DPI = dry powder inhaler; GI = gastrointestinal; HF = heart failure; HPA = hypothalamic-pituitary-adrenal; IgE = immunoglobulin E; IM = intramuscular; INR = international normalized ratio; IV = intravenous; LFT = liver function test; MDI = metered-dose inhaler; PO = oral; prn = as needed; SC = subcutaneous; SCR = serum creatinine