Adult asthma: Diagnosis and treatment

Abstract: Adult asthma is a prevalent chronic medical condition that is associated with high morbidity, mortality, and cost. Early identification, evidence-based diagnosis, and step-wise management can lead to improvements in patient outcomes, decrease exacerbations, and eliminate respiratory function decline as the patient ages.

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Adult asthma is a prevalent chronic condition characterized by recurrent episodes of airflow obstruction associated with bronchial hyperresponsiveness and chronic airway inflammation. This obstruction is generally reversible, which differentiates asthma from other respiratory conditions. Although the obstruction is reversible, failure to address symptom control and prevent exacerbations can lead to a decline in respiratory function, increasing asthma morbidity and mortality. This article provides an overview of the epidemiology, pathophysiology, diagnosis, and management of adults with asthma for the primary care provider (PCP) utilizing current evidence-based guidelines.

Epidemiology
In the United States, approximately 18 million individuals over age 18 (7.7%) are living with asthma. The prevalence of asthma peaks in early adolescence and decreases with age, declining to approximately 6.6% in individuals over age 65. However, the prevalence of asthma increases in females over age 18 (9.7%) compared with females under age 18 (6.9%). The inverse is true for males, as 9.9% under age 18 are diagnosed with asthma compared with 5.4% of males over age 18. A higher prevalence of asthma is seen in Black adults (9.1%) compared with White adults (7.9%) in the United States.

The burden of asthma is significant in terms of morbidity, mortality, and cost. In adults over age 18 living with asthma, 46.6% have experienced at least one asthma attack, and 13% have been hospitalized. Hospitalization rates are disproportionate, with hospital admission of Black adults at almost 30% compared with almost 9% of White adults with asthma.

Although the overall rate of asthma mortality has decreased each year since 2001 at a rate of over 3% per year, asthma mortality increases with age and remains approximately 10%. Medical cost related to increasing asthma morbidity and mortality in the United States is an estimated $56 billion. From 2002 to 2007, asthma was estimated to cost over $3,000 per individual per year. In 2012, over 10 million provider office visits were due to asthma, and 1.6 million ED visits were secondary to asthma in 2013.

In addition to medical cost, loss of productivity is significant with asthma. Asthma exacerbated by work-related exposures and conditions affects approximately 25% of adults with asthma. One-third of adults with asthma miss work...
or school. Additional cost is attributed to decreased work productivity, increased number of sick days, and higher unemployment.

Given the prevalence of asthma and its burden on morbidity, mortality, cost, productivity, and potential adverse reactions, it is important for the PCP to use current evidence to develop adult treatment plans. Two comprehensive reports are available to help PCPs improve assessment, diagnosis, and management of patients with asthma: the 2007 National Heart, Lung, and Blood Institute (NHLBI) Expert Panel Report and the 2017 Global Initiative for Asthma (GINA) Global Strategy for Asthma Management and Prevention.

■ Pathophysiology
Airway limitation related to inflammation, bronchoconstriction, airway hyperresponsiveness, mucus production, and edema are the underlying etiologies of common asthma signs and symptoms. Activation of inflammatory cells and mediators as well as an altered immune response contribute to the underlying inflammation, which is the primary underlying physiologic change associated with asthma. There are often no or mild symptoms associated with the underlying inflammation. This leads to increases in airway hyperresponsiveness to irritants such as allergens, respiratory infections, and exercise. Asthma is characterized by reversible airflow limitation, but in the presence of chronic airway remodeling, there may be only partially reversible airflow limitation.

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<th>Asthma allergens and triggers</th>
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<td>• Dust and dust mites</td>
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<td>• Animal fur/dandruff</td>
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<td>• Cockroaches</td>
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<tr>
<td><strong>Triggers</strong></td>
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<td>• Exercise</td>
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<td>• Infection</td>
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<td>• Changes in weather</td>
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<td>• Menstrual cycle</td>
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<td>• Stress or strong emotions</td>
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<td>• Work conditions/exposures</td>
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<td>• Smoke</td>
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<td>• Chemicals</td>
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<tr>
<td>• Comorbid conditions (such as GERD, rhinitis, sinusitis)</td>
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<td>• Medications (such as aspirin, NSAIDs, ACE inhibitors, beta-blockers)</td>
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■ Clinical evaluation
**Chief complaint and history.** Asthma is often a lifelong chronic condition; understanding the historical pattern of typical onset and recurrence of symptoms is crucial. The chief complaint and history of present illness typically reveals a recurrent pattern of cough, wheezing, chest tightness, and dyspnea. Symptoms are typically worse at night or upon waking and with exposures to triggers and allergens (see Asthma allergens and triggers).

Adults with asthma may also present with multiple respiratory symptoms that may be associated with an upper respiratory infection. Asthma symptoms often occur concurrently with respiratory infections, and the symptoms can be very similar. Assessing the pattern of symptoms to include onset, duration, frequency, and seasonal and diurnal variations is critical in distinguishing the diagnosis of asthma from other conditions. Assessing medical history, current medications, allergies, family history, and social history also provides key findings that support the diagnosis of asthma.

**Medical and social history.** Diagnoses associated with asthma or the potential to precipitate asthma include gastroesophageal reflux disease (GERD), obstructive sleep apnea (OSA), allergic rhinitis, sinusitis, atopic dermatitis, and nasal polyps. If the onset of symptoms occurs later in life, especially in the presence of tobacco use and other nonasthma symptoms, the likelihood of asthma decreases, and alternative diagnoses are to be considered.

Assessing for allergies may reveal potential asthma triggers or medication intolerance related to the worsening of asthma. A family history of atopic dermatitis, allergies, and asthma may increase the risk of developing asthma. A family history of a first-degree relative with asthma with or without atopic dermatitis increases the risk of developing asthma (odds ratio ranging from two to four); however, atopic dermatitis alone may not be as strong a risk factor, especially if only one relative or a non-first-degree relative is affected. A thorough social history can help identify potential triggers such as tobacco, exercise, work, environmental exposures, and stress.

**Medications.** Assessing current medications may reveal potential triggers, such as aspirin, nonsteroidal anti-inflammatory drugs (NSAIDs), angiotensin-converting enzyme (ACE) inhibitors, and beta-blockers. Aspirin may induce respiratory symptoms up to 3 hours after ingestion and affects approximately 20% of adults with asthma. In less than 10% of individuals with an aspirin sensitivity, a cross sensitivity with both acetaminophen and NSAIDs may occur.

The pathophysiology of aspirin-induced asthma is not well defined but is likely related to an increase in leukotrienes...
and inflammatory factors. Similar to aspirin, ACE inhibitors are associated with an increase in proinflammatory mediators in the lung tissue, which can lead to inflammation, cough, wheezing, and dyspnea. However, studies have not found a correlation with worsening pulmonary function and clinical symptoms with ACE inhibitor therapy in patients with asthma.

Because of possible adverse respiratory effects in patients with asthma taking an ACE inhibitor, an angiotensin II receptor blocker (ARB) may be substituted because ARBs are not associated with an increase in inflammatory mediators in the lungs. Beta-blockers have been associated with an increase in bronchoconstriction and a decline in pulmonary function; however, their effect on signs and symptoms may not be as significant. The greatest decline in lung function is associated with nonselective beta-blockers and is dose-dependent. In the presence of asthma, cardioselective beta-blockers are an option for patients with strong clinical indications at the lowest effective dose.

**Physical findings.** Physical exam findings associated with asthma can vary significantly depending on the severity of asthma, if an exacerbation is present, and the presence of other associated diagnoses. The most frequent finding is expiratory wheezing. The absence of wheezing does not rule out asthma or an exacerbation. Patients presenting with asthma, not in an acute exacerbation, often have a completely normal physical exam. With an exacerbation, the pulmonary exam may reveal chest hyperexpansion, accessory muscle use, retractions, and a prolonged expiratory phase.

In severe exacerbations, additional physical exam findings may include hypoxia, tachypnea, tachycardia, tripod position (seated position with bilateral arms extended to knees to support the chest), pulsus paradoxus, and the absence of wheezing in imminent respiratory failure. Crackles and inspiratory wheezing are not consistent with asthma and should warrant alternative diagnoses. Extrapulmonary findings may include rhinitis, nasal polyps, cobblestone appearance of the posterior oropharynx, and atopic dermatitis.

### Diagnosing asthma

The diagnosis of asthma is based on history, physical exam, and diagnostic testing. Diagnostic testing indicated for diagnosis or monitoring of asthma may include spirometry, peak expiratory flow (PEF), bronchial provocation, and chest X-ray. Peak flow meters that measure PEF are easy to use and widely found in primary care offices. Many primary care offices offer spirometry (which also allows for bronchial provocation). Blain and Craig found that almost half of the family practice providers and 60% of the internal medicine practices they studied had the necessary equipment to utilize spirometry. Of the offices without spirometry, the majority referred patients to a hospital for spirometry, with only 6% referring to a specialist for spirometry.

**Spirometry** measures obstruction and severity of asthma and confirms chronic airflow limitation by assessing forced expiratory volume in 1 second (FEV₁), forced vital capacity (FVC), and FEV₁/FVC, which represents the proportion of the vital capacity (maximum amount of air expelled from the lungs) an individual expires in the first second of forced expiration. Spirometry should be obtained to determine respiratory obstruction and reversibility in patients age 5 years and older. Diagnosis and reversibility are determined by obtaining pulmonary function measures prior to and after (10 to 15 minutes) inhalation of a short-acting beta2-agonist (SABA). (See Interpretation of spirometry findings.)

The NHLBI recommends that spirometry be repeated after treatment has started and symptoms have stabilized to allow for documentation of the patient’s normal level of lung function; again during times of persistent diminished asthma control or if asthma symptoms progress; then on a routine basis every 1 to 2 years to assess progression of airway disease.

**PEF**, most often measured by a peak flow meter, is not generally considered diagnostic; it is best suited to monitor asthma. If spirometry is not available, a change in PEF
of 20% (or excessive variability between attempts greater than 10%) in adults in twice-daily PEFs over 2 weeks is considered adequate for the diagnosis of asthma. The GINA guidelines recommend short-term PEF measurements after diagnosis to identify changes in respiratory function, assess the need for adjustment in management (PEF variation greater than 10%), establish a response to treatment, determine triggers, and/or establish a baseline for an asthma action plan. Long-term monitoring of PEF is recommended for patients who have moderate or severe persistent asthma, frequent exacerbations, are unable to accurately perceive limitation in airflow, or those who prefer this monitoring method.

**Bronchial provocation test** (also known as bronchial challenge test) is used to determine airway hyperresponsiveness. Bronchial provocation can be useful when asthma is a differential diagnosis, but spirometry is near normal or normal. This test is considered moderately sensitive with low specificity for the diagnosis of asthma. Therefore, a positive test can signify asthma, but it can also be indicative of other diagnoses (allergic rhinitis, chronic obstructive pulmonary disease [COPD], or cystic fibrosis); conversely, a negative test supports ruling out asthma as a diagnosis.

**Chest X-ray.** Chest X-rays are not recommended to routinely assess or diagnose asthma. Typically, a chest X-ray is normal or possibly displays hyperinflation. A chest X-ray is only recommended when other conditions are suspected beyond asthma, such as cardiopulmonary diagnoses in older adults.

**Special considerations.** Sputum eosinophil counts, fractional exhaled nitric oxide (FeNO), and allergy testing are not recommended routine assessment tools in the diagnosis and treatment of asthma for the general population. Sputum-guided treatment is recommended for patients with moderate or severe asthma not responding to a high-dose inhaled corticosteroid (ICS) or ICS and a long-acting beta2-agonist (LABA) and are referred to specialty medical offices that have access to and are experienced with this type of testing. Allergy testing may reveal sensitivity to certain triggers, but this does not determine if those triggers cause asthma symptoms. Elevated FeNO in nonsmokers without specific respiratory symptoms may indicate eosinophilic asthma and a potential for positive short-term results of ICS use, but this finding may also designate nonasthma-related diagnoses such as allergic rhinitis and is therefore not considered valuable in diagnosing asthma.

There are specific considerations when approaching certain populations or scenarios that may vary the testing order or recommendations (see Special considerations).

### Nonpharmacologic management

**Medication health literacy.** Ensure good communication with the patient and family, and ensure they have a good understanding of the patient’s medication regimen, when to take the prescribed medication, which medications are daily/controllers versus those that are fast/rescuers, when to adjust medications, and when to seek medical attention. Examples of helpful health literacy strategies include the provider actively listening to help the patient feel comfortable asking for clarification; observing for visual cues that may indicate confusion or discomfort; starting with the most important information and avoiding the use of complex numerical

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**Assessing current medications may reveal potential asthma triggers, such as aspirin, NSAIDs, ACE inhibitors, and beta-blockers.**
Medication class and category\textsuperscript{10,20}

Consult the manufacturer’s prescribing label for complete prescribing information for each drug.

Relievers (short-term control)
- SABAs (albuterol [preferred drug] and levalbuterol can be added to SABA)
- SAMA (ipratropium for moderate-severe exacerbations)
- Systemic corticosteroid burst (prednisone or prednisolone added to SABA for severe acute exacerbation)

Controllers (long-term control)
- ICS (beclomethasone, budesonide, ciclesonide, flunisolide, fluticasone, mometasone)
- ICS/LABAs (budesonide/formoterol, fluticasone/salmeterol, fluticasone/vilanterol, mometasone/formoterol [LABA should not be used alone without ICS for asthma])
- LTRAs (montelukast, zafirlukast, zileuton)

Add-on therapies (long-term control)
- LAMA (tiotropium)
- Anti-IgE antibody (omalizumab)
- IL-5 inhibitors (mepolizumab, reslizumab)
- Systemic corticosteroids
- Methylxanthine (sustained-release theophylline)

Avoidance and prevention. Avoidance of known environmental triggers can help manage asthma and decrease exacerbations.\textsuperscript{1,10} Examples include smoking cessation (patient and family); avoiding pets, chemicals, and environmental and occupational exposures that are triggers; and removing or limiting carpets and upholstered furniture in the home. Use of allergen-impermeable mattresses and pillow covers and weekly washing of linens and pets can also be helpful.\textsuperscript{1} If asthma is related to allergens, allergen immunotherapy may be considered but has limited documented efficacy in the management of asthma.\textsuperscript{1,10}

Treatment and control of certain comorbid conditions can improve asthma management and quality of life. These conditions include anxiety and depression, OSA, GERD, obesity, and rhinitis/sinusitis.\textsuperscript{10} Screening patients for these conditions when appropriate may improve asthma control.

Asthma medications fall into two main categories: relievers for short-term symptom relief (also referred to as rescue) and controllers for long-term management. Controllers are often differentiated into usual and late-stage controllers (add-on therapies). (See Medication class and category.)

Relievers. SABAs are the mainstay of treatment for acute asthma symptoms.\textsuperscript{10} Albuterol is the most common medication prescribed in this class and is available as a dry powder inhaler (DPI), metered-dose inhaler (MDI), and nebulizer (NEB) solution. Although levalbuterol is the R enantiomer of albuterol (racemic mixture with equal parts of R and S enantiomers) and the primary contributor to albuterol’s pharmacologic bronchodilating activity, it does not offer any clear benefit in regards to an improved airway response nor adverse-reaction profile at therapeutic doses when compared with albuterol.\textsuperscript{18}

An MDI plus a spacer is better at dose delivery compared with an MDI alone and equivalent to nebulizer treatments.\textsuperscript{1,10} For bronchospasm, the usual dose for albuterol MDI is 2 puffs every 4 to 6 hours as needed.\textsuperscript{20} The intensity
and duration of SABAs are dose-dependent. Higher doses may be needed for full relief of symptoms.20

Ipratropium, a short-acting muscarinic antagonist (SAMA), can be used in addition to albuterol. There is evidence for using ipratropium for rescue in the ED with modest benefit in improving lung function and a decreased need for hospital admission.21 It can also be used as an alternative to a SABA for patients with intolerable adverse drug reactions to a SABA (tachycardia, dysrhythmia, or tremors).

In patients with an incomplete or poor (persistent or marked wheezing and dyspnea) response to inhaled SABA following an exacerbation, a timely short course or burst of systemic corticosteroids may improve the response to an acute exacerbation and can often prevent an ED visit or hospitalization. Even shortening the time to administration by less than 1 hour has shown benefits in admission rates in the ED.22 Time to peak serum levels for oral corticosteroids is 1 to 3 hours, so it is prudent to begin therapy as soon as possible.20

There is no evidence to suggest an added benefit of I.V. versus oral corticosteroids. The I.V. route is reserved for patients in the emergency setting with limited ability to take oral medications, such as those who are obtunded, endotracheally intubated, or too dyspneic to swallow medications. The burst should be continued until symptoms resolve and PEF is at least 80% of personal best. Adverse reactions include increases in blood glucose levels, appetite, and BP. These drugs may also alter mental status, including worsening psychosis and insomnia.20

In patients who are uncontrolled on a high-dose ICS plus a LABA, adding tiotropium daily should be considered.

Controllers. ICSs are the drugs of choice for controlling asthma-related inflammation.10 Benefits include a decrease in symptoms, improved lung function and quality of life, and decreased risks of asthma exacerbations, hospitalizations, and death. There are a variety of corticosteroids categorized as low-, medium-, and high-intensity based on dosing.1

Three different LABA are currently available for use in the treatment of asthma. Formoterol and vilanterol have a relatively quick onset of action at approximately 5 minutes, and salmeterol starts working in about 20 minutes.20

Salmeterol and formoterol work for 12 hours, and vilanterol has a 24-hour duration.20 Common adverse reactions of LABAs are similar to SABAs; however, LABAs have a black box warning due to an increased risk of severe asthma exacerbations and death in postmarketing surveillance studies.23 As a result, the FDA is requiring follow-up prospective studies; initial results indicate no difference in safety or asthma-related events (hospitalization, intubation, and death) when a LABA is added to an ICS compared with an ICS alone. The use of a LABA without an ICS is not recommended.23 Benefits of the combination of a LABA with an ICS include comparable benefits in lung function and asthma symptoms at lower doses of the ICS.19

Three leukotriene receptor antagonists (LTRAs) are indicated for control of asthma: montelukast, zafirlukast, and zileuton. Their onset of action is 30 minutes, peak at 1 to 2 hours, and it may take weeks before maximum benefits are seen. Benefits include a steroid-sparing effect and a reduction in exercise-induced bronchospasms. They are less effective than an ICS and a LABA in combination with an ICS but may be appropriate for patients who are unable or unwilling to use an ICS or have concurrent allergic rhinitis.10

Montelukast may have an advantage for the PCP over other LTRAs due to the number of dosage forms available indicated over a wide age range and fewer adverse reactions, drug-drug, and drug-food interactions. Therefore, zafirlukast and zileuton may be best reserved for asthma specialists.20

There are drug/drug and drug/food interactions to consider before prescribing LTRAs. Phenobarbital may decrease montelukast levels. Zafirlukast’s bioavailability is dramatically (40%) decreased if taken with food and may increase international normalized ratio (INR) if given with warfarin. Zileuton can also increase INR with warfarin and may also increase theophylline levels. LTRAs are generally well tolerated but may have significant adverse reactions, including increase in liver function tests, headache, dyspepsia, myalgia, weakness, respiratory infections, restlessness, abnormal dreams, and hypersensitivity reactions.20

Add-on therapies for severe asthma. Several inhaled long-acting muscarinic receptor antagonists (LAMAs) are available for COPD, and tiotropium bromide inhalation spray for oral inhalation is approved by the FDA for long-term management of asthma in patients age 6 years and older.20,24 Adding tiotropium to a medium-dose ICS for asthma can provide a similar benefit to lung function as adding a LABA; however, it does not reduce hospitalizations nor improve quality of life. The 2017 GINA guidelines recommend tiotropium late in the stepwise approach to therapy (step four or five) in severe asthma that is uncontrolled despite two or more controllers.20,20

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In patients who are uncontrolled on a high-dose ICS plus a LABA, adding tiotropium daily should be considered. In patients who cannot tolerate a LABA, tiotropium can be added to the high-dose ICS and an LTRA.24

Serious but rare adverse reactions of tiotropium include bronchospasms and angioedema. The most common adverse reactions include sore throat, bronchitis, sinus infection, bitter taste, and headache. Tiotropium use can lead to typical anticholinergic adverse reactions, such as dry mouth, blurred vision, increased intraocular pressure, urinary retention, constipation, and dizziness.20,24

Other add-on therapies for uncontrolled severe asthma include three different monoclonal antibodies: omalizumab (an anti-immunoglobulin E [IgE] antibody), mepolizumab (an interleukin-5 [IL-5] antagonist monoclonal antibody [IgG1 kappa]), and reslizumab (an IL-5 antagonist monoclonal antibody [IgG4 kappa]). These agents are usually reserved for specialists due to both required injections and potential serious adverse reactions and are not covered in this article.

Long-term systemic corticosteroids dosed either every day or every other day can be used in severe asthma; however, the lowest possible dose is preferred due to their extensive systemic-related adverse-reaction profile.10 Adverse reactions include increased BP, hyperglycemia, weight gain, gastrointestinal bleeding and ulcers, cushingoid signs, cataracts, and muscle aches. Long-term use decreases immune response, growth, bone density, and hypothalamic pituitary adrenal axis suppression.20

Medication delivery selection. Once a particular controller class is identified as appropriate, there are several factors to consider when selecting a particular medication. It is key to appreciate the advantages and disadvantages of each delivery method: NEB, MDIs, MDI plus holding chamber, and DPIs. NEBs deliver high doses and patient coordination is not required, but they lack portability and require a long administration time. MDIs are portable and compact, do not require drug/device preparation, are administered over a short period of time, and lack the risk of contamination.

Disadvantages of MDIs include the required coordination of inhalation and actuation of the propellant/medication. DPIs are small, portable, and have dose counters. On the downside, they require adequate inspiratory flow rates (30 to 120 L/min depending on the device) to properly draw the medication into the lungs.25

Guidelines suggest providing device education and proper technique with written instruction to every patient.1,10 Providing feedback or correction of technique as appropriate is necessary. Providing patients with supplemental video instructions may be a good method of educational reinforcement. Proper technique should be verified at each follow-up visit. Repeating instructions is much more likely to insure proper device use.26

### Summary
A stepwise approach to making the diagnosis of asthma and consideration of special populations ensures accurate and timely intervention. An evidence-based and systematic approach to medication management and patient engagement is a safe and effective means to reduce asthma symptoms, exacerbations, and decline in respiratory function.  

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**Add-on therapies for uncontrolled severe asthma include the monoclonal antibodies omalizumab, mepolizumab, and reslizumab.**

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