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Diagnosis and Management of Asthma in Adults
A Review

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IMPORTANCE Asthma affects about 7.5% of the adult population. Evidence-based diagnosis, monitoring, and treatment can improve functioning and quality of life in adult patients with asthma.

OBSERVATIONS Asthma is a heterogeneous clinical syndrome primarily affecting the lower respiratory tract, characterized by episodic or persistent symptoms of wheezing, dyspnea, and cough. The diagnosis of asthma requires these symptoms and demonstration of reversible airway obstruction using spirometry. Identifying clinically important allergen sensitivities is useful. Inhaled short-acting β_2-agonists provide rapid relief of acute symptoms, but maintenance with daily inhaled corticosteroids is the standard of care for persistent asthma. Combination therapy, including inhaled corticosteroids and long-acting β_2-agonists, is effective in patients for whom inhaled corticosteroids alone are insufficient. The use of inhaled long-acting β_2-agonists alone is not appropriate. Other controller approaches include long-acting muscarinic antagonists (eg, tiotropium), and biological agents directed against proteins involved in the pathogenesis of asthma (eg, omalizumab, mepolizumab, reslizumab).

CONCLUSIONS AND RELEVANCE Asthma is characterized by variable airway obstruction, airway hyperresponsiveness, and airway inflammation. Management of persistent asthma requires avoidance of aggravating environmental factors, use of short-acting β_2-agonists for rapid relief of symptoms, and daily use of inhaled corticosteroids. Other controller medications, such as long-acting bronchodilators and biologics, may be required in moderate and severe asthma. Patients with severe asthma generally benefit from consultation with an asthma specialist for consideration of additional treatment, including injectable biologic agents.

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Asthma affects about 7.5% of adults in the United States, resulting in 1.8 million hospitalizations and 10.5 million physician office visits per year (**Table 1**). Asthma is more common in black (8.7%) and Puerto Rican Hispanic (13.3%) individuals than in white individuals (7.6%) and is associated with higher mortality in blacks than in whites (25.4 vs 8.8 per million annually) (Table 1). Inhaled corticosteroids increase the number of days without symptoms (by 7-21 d/mo), improve lung function (forced expiratory volume in first second of expiration [FEV_1]) by 13% and peak flow by 23 to 41 L/min,[7] and reduce symptoms of dyspnea, cough, and nighttime awakening.[8]

Asthma exhibits considerable clinical and molecular heterogeneity (eg, atopic vs nonatopic, aspirin-exacerbated respiratory disease, obesity-associated asthma), which complicates diagnostic evaluations and affects therapeutic responsiveness.[9] For example, patients with asthma who smoke have relative resistance to inhaled corticosteroids.[10] Patients with asthma uncontrolled by standard treatment and with peripheral blood eosinophilia may benefit from mepolizumab or reslizumab, and those with elevated perennial allergen-specific IgE could be candidates for omalizumab.[11] Clinical history, spirometry, and assessment of allergic sensitivities are important for diagnosis of asthma.[12,13]

This review presents an evidence-based approach to the diagnosis and management of mild to moderate stable asthma in adults. For patients with severe disease, generally manifested as continuing symptoms and airway obstruction despite appropriate therapy,[12,13] consultation with an asthma specialist (allergist or pulmonologist) should be sought.

Methods

The Cochrane Database of Systematic Reviews, Cumulative Index to Nursing and Allied Health Literature (CINAHL), EMBASE, MEDLINE, Population Information Online, PubMed, and Web of Science were searched for the period from the inception of each database through March 2017 for randomized clinical trials, systematic reviews, and/or meta-analyses and for observational studies using *asthma* or *anti-asthmatic drugs* or *asthma management or therapeutic* as primary search terms. Titles and abstracts of the articles were initially screened, and selected articles underwent full review. The bibliographies of selected articles were manually screened for additional relevant articles. All authors agreed on the final bibliography. Emphasis was given

Table 1. Prevalence, Mortality, and Health Care Utilization Among Adults With Asthma in the United States

Measure	Value
Prevalence, %[a]	
Overall prevalence	7.4
Sex	
Male	5.1
Female	9.6
Race/ethnicity	
White non-Hispanic	7.6
Black non-Hispanic	8.7
Hispanic	5.8
Others	6.8
Hispanic of Puerto Rican origin	13.3
Hispanic of Mexican origin	4.9
Asthma-Specific Mortality (Deaths per Million per Year)[b]	
Overall	14.1
Race/ethnicity	
White non-Hispanic	8.8
Black non-Hispanic	25.4
Hispanic	7.7
Others	9.9
Health Care Utilization	
Inpatient discharges (rate per 10 000 per year)[c]	
Overall	13.0
Race	
White	8.7
Black	29.9
Other	12.6
Emergency department visits (in millions per year)[d]	1.8
Physician office visits (in millions per year)[e]	10.5
Hospital outpatient department visits (in millions per year)[f]	1.3

[a] Asthma prevalence by age, sex, and race/ethnicity as reported in 2014 National Health Interview Survey.

[b] Asthma mortality (deaths per million) as reported in 2014 National Centers for Health Statistics surveys. Death rates by age are age-adjusted to 2000 US Standard Population.

[c] Inpatient discharges as reported in the 2010 National Hospital Discharge Survey.

[d] Emergency department visits as reported in the 2013 National Ambulatory Medical Care Survey.

[e] Physician office visits as reported in the 2012 National Ambulatory Medical Care Survey.

[f] Hospital outpatient department visits as reported in the 2010 National Hospital Ambulatory Medical Care Survey.

to randomized clinical trials and articles that included information of interest to a general medical readership.

Results

Clinical Presentation

Asthma is a heterogeneous clinical syndrome affecting the lower respiratory tract. It presents as episodic or persistent symptoms of wheezing, dyspnea, air hunger, and cough. Symptoms may be precipitated or exacerbated by exposure to allergens and irritants, viral upper respiratory tract infections, bacterial sinusitis, exercise, and cold air. Nocturnal symptoms indicate more severe disease, causing awakening in the early morning hours (for those with a normal diurnal schedule). The clinical presentation of asthma is variable with respect to severity, underlying pathogenic mechanisms, effect on quality of life, and responsiveness to treatment.[9]

Asthma may develop at any age, although onset is more frequent in childhood and young adulthood. Familial clustering occurs, suggesting that genetic factors are important.[12-16] Risk factors for asthma include heredity, exposure to environmental tobacco smoke, viral infections in the first 3 years of life, and socioeconomic factors such as income level, the presence of cockroach or rodent infestations in the home, and access to medical care.[12] Heritable factors include genes regulating IgE-related mechanisms,[12,13] glucocorticoid response,[14] airway smooth muscle development (*ADAM33*),[15] and components of the immune system (*HLA-G*).[16] Tobacco smoke is a common exacerbating factor in patients with asthma.[13]

Physical findings in stable asthma are nonspecific, and physical examination findings can be normal when the patient is well. Poorly controlled asthma may exhibit auscultatory wheezing or rhonchi, but the intensity of wheezing is a poor indicator of the severity of either airflow obstruction or disease pathology. In an acute exacerbation of asthma, tachypnea, pulsus paradoxus (eg, a decrease of more than 10 mm Hg in systolic blood pressure during inspiration), cyanosis, and use of accessory muscles of respiration may be evident.

The term "exacerbation" may be used to indicate a short-lived worsening of symptoms managed effectively with short-acting β_2 agents. It also may be used to indicate a more serious deterioration of lung function, of longer duration, associated with increased symptoms and commonly precipitated by exposure to allergens or viral infections, that may require intensification of anti-inflammatory therapy.[12,13]

Atopic or allergic asthma is frequently associated with allergic rhinitis and conjunctivitis. Food allergies and atopic dermatitis may also be observed. Nonatopic asthma, defined as not associated with allergies, is less frequent than atopic asthma in patients with mild asthma (20%) or severe asthma (29%)[17] and is more common in older adults compared with children; its evaluation and pharmacologic management are otherwise similar to that for atopic disease.[12,13]

Adverse consequences of systemic steroid treatment may occur if frequent courses of systemic steroid therapy are necessary (**Table 2**). Allergic bronchopulmonary mycoses, including allergic bronchopulmonary aspergillosis, may have a prevalence as high as 25% among people with asthma,[31] although the pathogenesis and causes of this complication remain uncertain.[12]

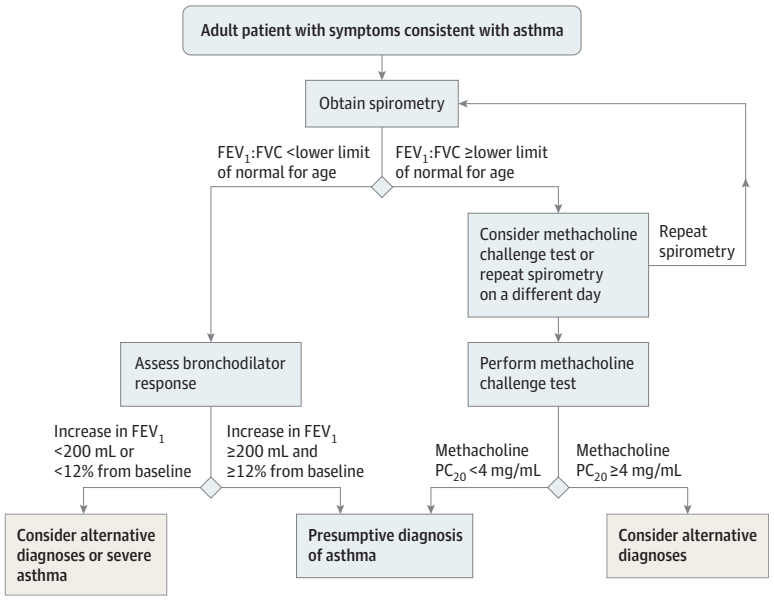
In the setting of the above symptom complex and airway obstruction reversible by β_2-agonists, the diagnosis of asthma can usually be made. A proposed algorithm for the diagnosis of asthma is presented in **Figure 1**. The combination of asthma-like symptoms and β_2 agonist–reversible bronchial obstruction usually is sufficient to establish the diagnosis of asthma. Appropriate diagnostic testing should be conducted to confirm a diagnosis of asthma or suggest alternatives. Diseases of the heart and great vessels, the pulmonary parenchyma, and the upper airway can mimic the clinical presentation of asthma (**Box**).

Table 2. Major Medical Therapies for Stable Asthma in Adults

Category	Examples	Usual Dosing	Treatment Effect	Adverse Effects	Notes
Standard Therapies					
Relievers					
Short-acting β_2-agonists (SABAs)	Albuterol Levalbuterol Pirbuterol	2 puffs every 4-6 h	Bronchodilation (7%-15% increase in FEV_1, dose dependent)	Nervousness, tremor, bronchospasm, tachycardia, headache, pharyngitis	
Short-acting muscarinic antagonists (SAMAs)	Ipratropium	2-3 puffs every 6 h	Bronchodilation (7%-15% increase in FEV_1, dose dependent)	Bronchitis, COPD exacerbation, dyspnea, headache	
Controllers					
Inhaled corticosteroids (ICSs)	Fluticasone	2 puffs twice daily	Decreased daytime and nocturnal symptoms Reduced exacerbations and death Improved FEV_1 (improvement in symptoms, exacerbations, death, and FEV_1 are all dose dependent[18,19])	Upper respiratory tract infection, throat irritation, sinusitis, dysphonia, candidiasis, cough, bronchitis, headache	Comparisons for low, moderate, and high doses of ICSs are detailed elsewhere[12,13]
	Budesonide	2-4 puffs twice daily			
	Mometasone	Varies by device			
	Ciclesonide	160-320 µg twice daily			
Leukotriene receptor antagonists (LTRAs)	Montelukast	10 mg daily	Decreased daytime and nocturnal symptoms Improved FEV_1[20]	Headache, fatigue, abdominal pain, dyspepsia, mood changes	
	Zafirlukast	20 mg twice daily			
Leukotriene synthesis inhibitor	Zileuton	600 mg 4 times daily	Improved FEV_1[21]	Headache, pain, abdominal pain, dyspepsia, nausea, myalgia, increased alanine aminotransferase	Requires monitoring of hepatic enzymes Drug interactions are common
Long-acting β_2-agonists (LABAs)	Salmeterol	2 puffs twice daily	Improved FEV_1[22]	Headache, rhinitis, bronchitis, influenza, dizziness	These agents should not be used without a simultaneous ICS agent
	Formoterol	2 puffs twice daily			
	Vilanterol	NA			
Long-acting muscarinic antagonist (LAMA)	Tiotropium	1 puff daily	Improved FEV_1[23]	Dry mouth, upper respiratory tract infection, pharyngitis, sinusitis, chest pain	
Combined ICSs/LABAs	Fluticasone/ salmeterol inhaler	1 puff twice daily	Benefits of both ICSs and LABAs[24]	Nasopharyngitis, URI, headache, sinusitis, influenza, back pain	
	Fluticasone/ salmeterol HFA	2 puffs twice daily			
	Budesonide/ formoterol	2 puffs twice daily			
	Fluticasone/ vilanterol	1 puff daily			
Other Therapies					
Oral corticosteroids	Prednisone	5-20 mg/d		Hypertension, increased appetite, weight gain, insomnia, mood changes, gastritis, skin atrophy, osteoporosis, adrenal suppression, avascular necrosis of bone	Doses listed are for chronic maintenance, not for exacerbations Daily use of oral corticosteroids is not recommended unless other options are ineffective; consult with an asthma specialist
	Methylprednisolone	4-16 mg/d			
Biologics					
Anti-IgE	Omalizumab	Varies by weight	Reduced asthma exacerbations Variable benefit in FEV_1[25]	Injection site reaction, viral infections, URI, sinusitis, headache, pharyngitis, anaphylaxis	Used primarily by asthma specialists
Anti-IL-5	Mepolizumab	100 mg subcutaneously monthly	Reduced asthma exacerbations Small improvement in FEV_1[26-29]	Headache, injection site reaction, back pain, fatigue, oropharyngeal pain	Used primarily by asthma specialists
	Reslizumab	Varies by weight, IV administration			
Bronchial thermoplasty		3 Bronchoscopic treatments, once monthly for 3 mo	Reduced asthma exacerbations, emergency department visits through at least 1 y[30]	Short-term worsening of asthma symptoms, cough, wheezing, chest pain, URI, infection	Specialty treatment Durability of benefit is controversial

Abbreviations: COPD, chronic obstructive pulmonary disease; FEV_1, forced expiratory volume in first second of expiration; URI, upper respiratory infection.

Figure 1. Proposed Algorithm for Initial Diagnosis of Asthma



The first diagnostic test should be forced expiratory spirometry, categorized as obstructed (ratio of forced expiratory volume in first second of expiration [FEV_1] to forced vital capacity [FVC] less than lower limit of normal) or not obstructed. If airway obstruction is present, a bronchodilator response following 2 to 4 puffs of short-acting β_2-agonist should be determined. Fixed or partially reversible airway obstruction suggests alternative diagnoses, although severe asthma may be present. PC_{20} indicates the methacholine concentration required to achieve a 20% decrease in FEV_1.

Box. Differential Diagnosis of Asthma

- Upper respiratory tract
  - Vocal cord dysfunction
  - Congestive rhinopathy
  - Obstructive sleep apnea syndrome
- Lower respiratory tract
  - Chronic obstructive pulmonary disease
  - Occupational bronchitis
  - Cystic fibrosis
  - Bronchiectasis
  - Pneumonia
- Gastrointestinal tract
  - Gastroesophageal reflux disease
- Cardiovascular system
  - Congestive heart failure
  - Pulmonary hypertension
  - Chronic thromboembolic pulmonary disease
- Central nervous system
  - Habitual cough

Pathophysiology

Variable Airway Obstruction

A cardinal feature of asthma is variable airway obstruction,[32] a variation in airway caliber over the time frame of minutes to days; it is due to bronchoconstriction, mucosal inflammation, and luminal secretions, and results in increased airflow resistance and work of breathing. In more severe or longstanding disease, the airway obstruction may be entirely fixed or incompletely reversible with bronchodilator treatment.[17] Bronchoconstriction occurs in airways that contain contractile airway smooth muscle. Enhanced parasympathetic cholinergic tone occurs in nocturnal asthma and can cause contraction of airway smooth muscle, increased mucus production, and increased airway obstruction.[33] Factors associated with mucus overproduction and inflammation (allergen exposures, viral or bacterial infections)[34] can also increase obstruction.

Airway Hyperresponsiveness

Airway hyperresponsiveness,[32] an exaggerated reduction in airway caliber after a stimulus, has been recognized as a hallmark of asthma from the time of Claudius Galen, a physician in about AD 150.[35] Although not specific, airway hyperresponsiveness is a virtually universal finding in asthma, and is associated with airway inflammation. Airway hyperresponsiveness may be induced by allergens (eg, pollen, animal danders),[36] chlorine,[37] pollutants (eg, sulfur dioxide),[38] diesel exhaust particulates,[36] and viral upper respiratory tract infections.[39] Genetic variation accounts for some associations of environmental exposure and airway hyperresponsiveness,[40] but specific genetic predispositions for airway hyperresponsiveness and other triggers remain poorly understood. Sympathetic control in the airway is mediated via β_2-adrenoreceptors expressed on airway smooth muscle,[41] which are responsible for the bronchodilator response to albuterol used in diagnosis and symptom relief and for longer-term bronchodilation facilitated by long-acting β_2-agonist controller agents.[42] (Short- and long-acting β_2-agonists are used for distinct purposes in asthma therapy.) Cholinergic pathways may further contribute to airway hyperresponsiveness[43] and are the basis for the efficacy of anticholinergic therapy[23,44] The methacholine challenge test uses inhaled methacholine, a direct cholinergic agonist, to evoke concentration-dependent airway smooth muscle contraction.[45] Bronchoconstriction at low concentrations of methacholine (typically <4 mg/mL) suggest increased airway hyperresponsiveness (Figure 1).

Airway Inflammation

Airway inflammation is recognized as a pathogenic factor in asthma.[46] Inflammation involves many different cells (eosinophils,

Figure 2. National Asthma Education and Prevention Program Approach to Classification of Asthma Severity

Components of severity		Classification of asthma severity (age ≥12 y)			
			Persistent		
		Intermittent	Mild	Moderate	Severe
Impairment	Symptoms	≤2 d/wk	>2 d/wk but not daily	Daily	Throughout the day
	Nighttime awakenings	≤2× mo	3-4× mo	>1× wk but not nightly	Often 7× wk
	Short-acting β_2-agonist use for symptom control (not prevention of EIB)	≤2 d/wk	>2 d/wk but not daily, and not more than 1× on any day	Daily	Several times per day
	Interference with normal activity	None	Minor limitation	Some limitation	Extremely limited
	Lung function Normal FEV_1: FVC ratio 20-39 y 80% 40-59 y 75% 60-80 y 70%	• Normal FEV_1, between exacerbations • FEV_1, >80% predicted • FEV_1: FVC normal	• FEV_1, >80% predicted • FEV_1:FVC normal	• FEV_1, >60% but <80% predicted • FEV_1:FVC normal	• FEV_1, <60% predicted • FEV_1:FVC reduced >5%
Risk	Exacerbations requiring oral systemic corticosteroids	0-1/y	≥2/y	≥2/y	≥2/y
		Consider severity and interval since last exacerbation Frequency and severity may fluctuate over time for patients in any severity category Relative annual risk of exacerbation may be related to FEV_1			
Recommended step for initiating treatment (see Figure 3 for treatment steps)		Step 1	Step 2	Step 3 and consider short course of oral systemic corticosteroids	Step 4 or 5 and consider short course of oral systemic corticosteroids
		In 2-6 weeks, evaluate level of asthma control that is achieved and adjust therapy accordingly			

An estimate of asthma severity on initial presentation is made on the basis of daytime and nocturnal symptoms, the frequency of need for short-acting β_2-agonists for relief of symptoms, the degree to which asthma interferes with normal activity, the degree of airway obstruction measured by spirometry, and the history of asthma exacerbations. On the basis of these factors, asthma can be categorized as intermittent, or persistent (mild, moderate, or severe). This categorization informs the initial therapeutic approach (Figure 3). EIB indicates exercise-induced bronchoconstriction; FEV_1, forced expiratory volume in first second of expiration; FVC, forced vital capacity.

Figure adapted from NAEPP.[12]

lymphocytes, mast cells, neutrophils) and is commonly initiated by allergen-dependent release of histamine and other mediators from mast cells[47] and subsequent infiltration of lymphocytes (particularly T-helper type 2 [T_H2]) and granulocytes into the airway.[48] IgE occupies a central role in the pathogenesis of allergic asthma; inflammatory responses are mediated by allergen-specific IgE, generated during allergic sensitization, and bound to mast cells which are activated by reexposure to allergen. Elevated levels of proinflammatory cytokines IL-4, IL-5, and IL-13 are observed.[49,50] Airway inflammation accentuates obstruction by promoting mucosal infiltration and edema, mucus secretion, and airway hyperresponsiveness; it also predisposes to exacerbations. Structural changes, termed airway remodeling, include increased smooth muscle mass,[51] goblet cell hyperplasia,[52] and lamina reticularis thickening.[51] The T_H2 hypothesis (activation of T_H2 cells) provides conceptual understanding of the development of inflammation associated with asthma.[53] More recently it has been recognized that type 2 innate lymphoid cells also contribute to eosinophilic airway inflammation. This phenomenon is termed "type 2 inflammation."[54] Eosinophilic inflammation and asthma may develop in the absence of overt allergy.[55] Endogenous anti-inflammatory mediators appear to be important in controlling and resolving airway inflammation in individuals without asthma, and these mechanisms may be insufficiently or ineffectively activated in asthma: eg, reduced production of the anti-inflammatory factors IL-10 and lipoxin A4 has been identified in patients with asthma.[56,57]

Activation of IL-17, $CD4^+$ T cells (T_H17 cells), and IL-12/IL-23 is distinct from type 2 factors noted above and is more closely associated with neutrophilic inflammation.[58] Neutrophil infiltration and activation contribute to the severity of uncontrolled and severe asthma, and neutrophilic inflammation is less responsive to standard therapies, making the neutrophil an attractive potential target for novel asthma therapy.[59]

Assessment and Diagnosis

The diagnosis and severity of asthma are established based on clinical criteria: history, physical examination, and evidence of either reversible airflow obstruction, or airway hyperresponsiveness (Figure 1).[12,13] The US National Asthma Education and Prevention Program (NAEPP) approach to classifying asthma severity is based on 2 domains: impairment and risk. The impairment domain includes measured airway obstruction, the frequency and intensity of daytime and nocturnal symptoms, frequency of short-acting β_2 agonist use for symptom relief, and interference of daily activities by symptoms. The risk domain assesses the frequency of exacerbations (**Figure 2**). These data collectively define both asthma severity and asthma control.[12,13] Physical findings of accessory muscle use or audible wheezing during normal breathing may be present only during times of asthma exacerbation and have poor negative predictive value to exclude the diagnosis of asthma.

Spirometry is the most important diagnostic procedure for evaluating airway obstruction and its reversibility. It should

Table 3. Diagnostic Modalities Useful in Diagnosis and Treatment of Stable Asthma in Adults

Diagnostic Modality	Suggests Asthma	Other Differential Features
Clinical history	Wheezing, coughing, chest tightness May only be present or worsened with exertion, upper respiratory infection, seasonal or perennial allergies Nocturnal cough, particularly 2 AM to 4 AM Need for short-acting β_2-agonist inhaler for relief of symptoms Personal or family history of atopy	Occupational exposures Dyspnea only on exertion may suggest COPD Family history is often positive in atopic asthma Seasonal variation of symptoms or asthma severity is consistent with atopic asthma
Spirometry	Airway obstruction evidenced by FEV_1:FVC ratio <lower limit of normal Demonstrated reversibility of obstruction by increase in FEV_1 ≥200 mL and ≥12% from baseline measure after inhalation of 2-4 puffs of short-acting β_2-agonist Normal spirometry findings are not inconsistent with asthma	Airflow limitation that is irreversible or partially reversible may suggest COPD, bronchiectasis, or other obstructive disease
Bronchoprovocation with methacholine	20% or more decrease in FEV_1 with after inhalation of low concentration (<4 mg/mL) of methacholine; used principally in patients with symptoms consistent with asthma but who exhibit normal pulmonary function tests	Specificity and positive predictive value are low Allergic rhinitis, congestive heart failure, chronic bronchitis may all exhibit increased methacholine response
Impedance oscillometry	Elevated airway resistance at 5 Hz, elevated area of reactance, increased resonant frequency (Fres), reactance at 5Hz more negative than predicted	Increased total airway resistance at 5 Hz in comparison with large-airway resistance at 20 Hz suggests small-airway disease
Chest radiograph or CT scan of thorax	Usually normal but can exclude other diagnoses such as emphysema, lung cancer, infiltrative diseases, pneumonia	Central bronchiectasis may suggest allergic bronchopulmonary aspergillosis
CBC	Eosinophilia, particularly >300/μL; results can inform selection for mepolizumab or reslizumab therapy	Eosinophil count <150 mitigates against use of anti-IL-5 therapies
Serum total IgE	Elevated in atopic asthma, not in nonatopic asthma; can inform selection of omalizumab therapy	IgE >1000 IU/mL: consider allergic bronchopulmonary aspergillosis, atopic dermatitis, and other allergic manifestations
Skin prick testing or serum-specific IgE for aeroallergens	Positive, particularly for perennial allergens, or seasonal allergens with corresponding seasonal variation in asthma symptoms; may be negative in nonatopic asthma; can inform omalizumab therapy Positive testing can guide allergen avoidance strategies[12]	Positive test for *Aspergillus fumigatus* or *A niger* suggests possibility of allergic bronchopulmonary aspergillosis
Fractional excretion of nitric oxide	Intermediate level: 25-50 ppb in patients aged ≥12 y High level: >50 ppb in patients aged ≥12 y	Low levels are not inconsistent with asthma Levels >20 may identify omalizumab-responsive patients

Abbreviations: CDC, complete blood cell count; COPD, chronic obstructive pulmonary disease; CT, computed tomography; FEV_1, forced expiratory volume in first second of expiration; FVC, forced vital capacity.

be performed in all patients in whom asthma is a diagnostic consideration. The maximal volume of air forcibly exhaled from the point of maximal inhalation (forced vital capacity, FVC), the volume of air exhaled during the first second of this maneuver (FEV_1), and FEV_1:FVC ratio are 3 key measures. An FEV_1:FVC ratio less than the lower limit of normal (0.7-0.8 in adults, depending on age) (Figure 2) indicates airway obstruction, although asthma may be present even without demonstrable airway obstruction (Figure 1). Reversibility of airway obstruction is indicated by an increase in FEV_1 of 200 mL or greater and 12% or greater from baseline after inhalation of short-acting β_2-agonists. In patients who have smoked cigarettes, distinguishing asthma with partially reversible obstruction from chronic obstructive pulmonary disease is challenging and has led to the description of an asthma–chronic obstructive pulmonary disease overlap syndrome, the existence and clinical importance of which is controversial.[60] No validated approaches for differentiating these entities has been identified. A low diffusing capacity for carbon monoxide suggests an element of emphysema rather than asthma. Pulmonary function testing is less informative when performed during exacerbations of asthma and is best obtained during times of disease stability.

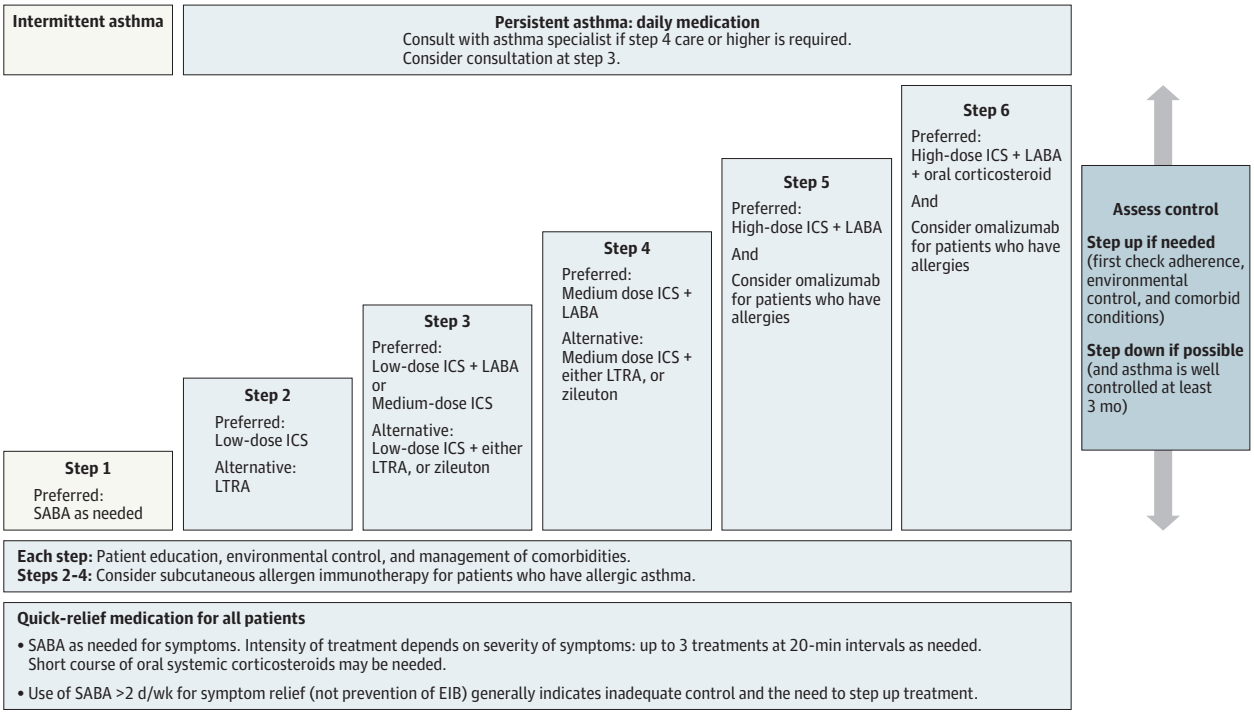
Bronchoprovocation with methacholine can be helpful in patients with suspected asthma and normal spirometry because a negative test result makes the diagnosis of asthma unlikely (Figure 1).[61] Outside the United States, mannitol may be used as an effective bronchoprovocation agent.[62] Methacholine and mannitol used as bronchoprovocation agents both have a sensitivity of approximately 80% and specificity of approximately 65%.[63]

Impedance oscillometry, a technique that measures airway resistance without forced expiration, can measure central and peripheral airway resistance in those patients for whom the forced expiratory maneuver is difficult or impossible, including elderly patients.[64] However, there is no consensus on the incremental value of impedance oscillometry over spirometry alone, nor are there sufficient data to establish the performance characteristics (sensitivity, specificity) of oscillometry vs spirometry alone in asthma.

In stable asthma, measurement of arterial blood gas values is rarely necessary, although it may be helpful in cases of acute decompensation and exacerbation. Periodic monitoring of pulse oximetry, with or without exercise, may be useful. Allergy evaluation has become increasingly important in recent years, as biologic agents have become available for treatment. A total serum IgE and specific IgE for common aeroallergens may be performed,[12,13] as these tests can guide allergen avoidance strategies and suggest the potential use of anti-IgE monoclonal therapeutics. Allergy skin testing may be substituted for serum measures of allergen-specific IgE.[12] A complete blood cell count with an elevated absolute eosinophil count can identify appropriate candidates for anti-IL-5 therapies (mepolizumab ≥150/μL and reslizumab ≥400/μL).

These diagnostic modalities are summarized in **Table 3**. The NAEPP[12] presents a severity classification system based on historical features and spirometric measurements, and recently updated Global Initiative for Asthma (GINA) guidelines are also now available.[13] Severity classes of intermittent, mild persistent, moderate persistent, and severe persistent asthma are defined, and severity categorization determines initial therapeutic approaches

Figure 3. National Asthma Education and Prevention Program Recommendations for Asthma Therapy



All patients with asthma should have a rescue inhaler composed of a short-acting β_2-agonist (eg, albuterol). Preferred initial therapy is outlined by step. Periodic reevaluation of asthma symptoms, lung function, and exacerbations is necessary to guide adjustments in treatment. Alphabetical order is used when more than 1 treatment option is listed within either preferred or alternative therapy. EIB indicates exercise-induced bronchoconstriction; ICS, inhaled corticosteroid; LABA, long-acting β_2-agonist; LTRA, leukotriene receptor antagonist; SABA, short-acting β_2-agonist.

Figure adapted from NAEPP.[12]

(Figure 3). The GINA guidelines also outline assessment of severity in patients already receiving effective controller therapy.[13]

Asthma symptom control, using validated patient questionnaires (Asthma Control Test [ACT], Asthma Quality of Life Questionnaire [AQLQ], or Asthma Control Questionnaire [ACQ]) to provide a quantitative assessment of symptoms, may be assessed at each visit.[12,65,66] (Because asthma symptoms and pulmonary function may not correlate well, measurement of both can inform adjustments to therapy.) Spirometry should be repeated every 1 to 2 years or with clinically significant change of asthma control to identify accelerated loss of lung function.[12] Home peak flow monitoring may be useful in some patients for whom routine office spirometry cannot be performed. Patients with relatively normal pulmonary function test results, but persistent symptoms (eg, abnormal ACT, ACQ, or AQLQ scores) may be candidates for intensification of treatment. Persistently abnormal findings from pulmonary function tests suggest the need for intensification of the controller regimen. The utility of routine monitoring of the concentration of exhaled nitric oxide has not been established; however, patients who are not receiving adequate doses of inhaled steroids may show elevated concentrations (ie, >50 ppb) of exhaled nitric oxide.[67]

There is little evidence to demonstrate the value of routine chest radiography in asthma. Chest imaging, beginning with a standard 2-view chest radiograph, may help to exclude other pulmonary pathology.[12] Patients who are older than 65 years, have a clinically important history of smoking or significant occupational exposures such as mineral or organic dusts, have persistent symptoms despite therapy, or present with long-standing disease may be at risk for chronic obstructive pulmonary disease or lung cancer.[12,13] The optimal imaging modality has not been established; low-dose, high-resolution computed tomographic scanning provides considerably more information than a standard chest radiograph, but with increased radiation exposure and higher cost.

Treatment

The goals of asthma treatment are reducing impairment (reducing symptoms, maintaining normal activities, achieving [nearly] normal pulmonary function test values) and minimizing risks associated with the disease (future exacerbations, medication adverse effects). Because of the heterogeneous nature of asthma and the limited availability of predictive biomarkers for treatment success, clinicians must approach patients with a guideline-based plan that recognizes specific environmental triggers and their mitigation (eg, allergens, viruses, or irritants encountered in occupational, household, or environmental settings), individual variability in the dose and particle size of inhaled corticosteroids, the class of long-acting bronchodilator (long-acting β_2 agonist vs long-acting muscarinic antagonist), and other individual factors to provide an individualized treatment plan. A written asthma action plan that details in lay language the signs and symptoms indicating worsening of asthma, such as increased dyspnea or cough, or need for more

frequent use of the β_2 agonist inhaler, and the steps required to mitigate that worsening, is a key component of management.

Pharmacologic options are classified as either reliever (short-term benefit) or controller (longer-term benefit) medications (Table 2). All patients with asthma should have access to a short-acting β_2 agonist inhaler (commonly albuterol) for treatment of acute symptoms; this intervention alone is appropriate for patients with intermittent asthma, defined as symptoms less than twice weekly with (near) normal pulmonary function. For patients with persistent asthma (defined as symptoms more than twice weekly or abnormal pulmonary function), a daily maintenance controller is generally appropriate. The initial choice of medication is directed by severity of asthma classification (intermittent; mild, moderate, or severe persistent [Figure 2]) at diagnosis. In the United States, guidelines recommend treatment based on 6 steps (Figure 3),[12] but the GINA guidelines define 5 steps, which are not strictly comparable to the US guidelines.[13]

In the US treatment guidelines, step 1 therapy is used for patients with intermittent asthma and consists of short-acting β_2-agonists, administered as needed. (These agents are also used for quick symptom relief in all patients with asthma, irrespective of severity.) Step 2 therapy is indicated for mild persistent asthma and preferably consists of low-dose inhaled corticosteroids, which improve asthma outcomes such as lung function, symptoms, and exacerbations[7,8,12,13] in a dose-dependent, but not necessarily dose-proportionate, manner (eg, a doubled dose of inhaled corticosteroids will not produce doubled improvement in lung function). The dose response to inhaled corticosteroids varies by the outcome measured (symptom reduction, lung function improvement, reduction in exacerbation).[12] Inhaled corticosteroids reduce the infiltration and activation of eosinophils, T_H2 cells, and other inflammatory cells. An oral leukotriene receptor antagonist may be as effective as inhaled corticosteroids and is an alternate first-line treatment.[68] These agents block the action of cysteinyl leukotrienes, key mediators of airway smooth muscle contraction.

Patients with moderate persistent asthma should start at step 3 therapy with medium-dose inhaled corticosteroids or a combination of low-dose inhaled corticosteroids and a long-acting β_2 agonist (Table 2). Longer-acting bronchodilators increase airway caliber for 12 to 24 hours. Spacers (large volume-holding chambers) may improve pulmonary delivery, reduce pharyngeal delivery, and reduce local adverse effects when used with compatible pressurized metered-dose inhaler systems, particularly for those patients for whom consistent coordination of inhalation with actuation of the device is a concern.

Patients diagnosed with severe persistent asthma, commonly characterized as near-continuous chest symptoms, the need for multiple inhalations daily of rescue β_2 agonist, nightly awakenings from asthma symptoms, or FEV_1 less than 60% predicted, should start at step 4, 5, or 6 and be referred for consultation with an asthma specialist (an allergist or pulmonologist).[12,13] Medication options for these patients include medium- or high-dose inhaled corticosteroid plus long-acting β_2 agonist combinations, inhaled long-acting muscarinic agonists (tiotropium),[23] and biologic therapy.[11-13]

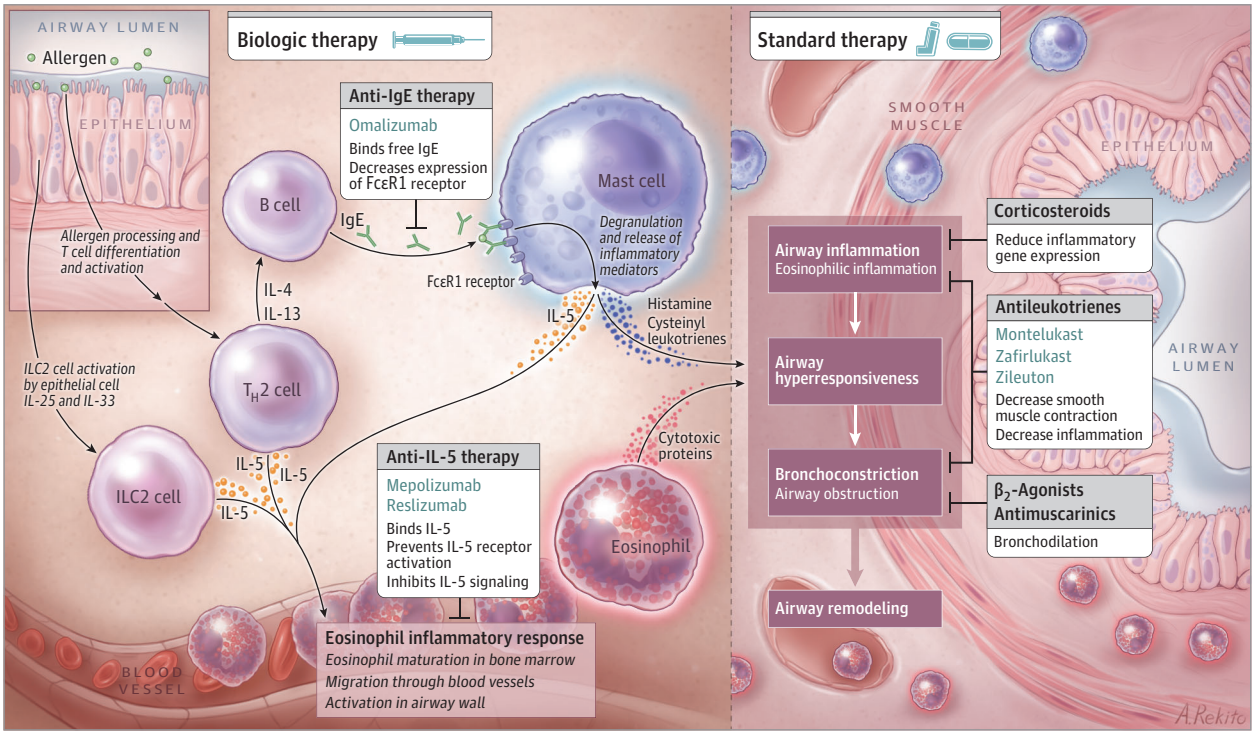
Long-acting bronchodilators should never be prescribed without an accompanying inhaled corticosteroid. The US Food and Drug Administration–approved package insert of each long-acting β_2 agonist contains a black box warning of the increased risk of adverse outcomes and death. However, recent prospective evidence suggests that long-acting β_2-agonists, when used appropriately (ie, always in combination with inhaled corticosteroids), do not confer adverse safety consequences and in fact reduce the risk of exacerbations and adverse events in adults with moderate to severe asthma compared with inhaled corticosteroids alone.[69]

For suboptimally controlled asthma, a physician should search for common problems such as incorrect inhaler technique, poor adherence, exposure to allergens, exposure to personal or secondhand tobacco smoke, gastroesophageal reflux, sinusitis, or intercurrent viral infections. If control is not optimal, intensification of the therapeutic regimen is usually indicated. The precise timing of follow-up visits is a matter of clinical judgment, as no prospective trials exist that directly address this question. Follow-up may range from several days or weeks for patients with very poorly controlled or severe disease, to months for patients with well-controlled, milder, and stable asthma. Once asthma is well controlled for 2 to 3 months, treatment may be stepped down to the lowest dose of medication that adequately controls symptoms and lung function.[12,13] Guidelines for deintensification of asthma therapy are not as well established as those for intensification, and there are no randomized clinical trials of step-down therapy on which to make specific recommendations.

For patients who continue to have uncontrolled asthma despite standard inhaled therapies, several parenteral biologic agents (monoclonal antibodies) are available. These agents act systemically by influencing the immunopathogenesis of asthma, rather than treating the consequences of inflammation and bronchospasm from within the airway, as standard controller therapies do (**Figure 4**). The central role of IgE in the pathogenesis of allergic airway disease makes IgE an attractive target for asthma therapy. Omalizumab is an anti-IgE monoclonal antibody used in allergic asthma accompanied by moderately elevated IgE level (30 to about 1000 IU/mL, depending on body weight) and evidence of sensitization to perennial aeroallergens. It reduces allergen-induced mast cell activation and decreases expression of IgE high-affinity receptors on mast cells[70] (Figure 4). Omalizumab is given by subcutaneous injection every 2 to 4 weeks, at a dose and frequency determined by body weight and serum IgE levels, and is principally effective in reducing exacerbations and need for oral steroids.[70] Retrospective analysis of omalizumab trials suggests that serum eosinophil counts in excess of 260/μL and fractional excretion of nitric oxide of at least 19.5 ppb may identify patients likely to improve with omalizumab. However, no biomarker has been subjected to rigorous prospective confirmation to determine its predictive value.[70] Little improvement in pulmonary function is observed, so lung function testing is not a good monitoring tool to assess omalizumab response. Measurement of serum IgE levels after initiating treatment is not useful. The primary clinical outcomes by which response may be judged are asthma exacerbations and symptoms.

Interleukin 5 is centrally involved in the synthesis, maturation, homing, and activation of eosinophils, suggesting a role for anti-IL-5 in managing eosinophilic airway disease. Anti-IL-5 monoclonal antibodies (mepolizumab and reslizumab) have recently been

Figure 4. Contrasting Standard vs Biologic Therapies in Asthma



Standard asthma therapy is commonly delivered via the airway, by therapeutic aerosols of inhaled corticosteroids (ICSs) or bronchodilators, and by design have effects largely limited to the environment of the airway. The cysteinyl leukotriene receptor (type 1) antagonist montelukast (and others) is delivered to the airway by the systemic circulation and reduces smooth muscle contraction and inflammation, particularly that due to activated eosinophils. Biologic therapy in asthma acts upstream of the inflammatory process in the airway.[11] Omalizumab reduces mast cell activation and release of mediators of bronchoconstriction (principally histamine and cysteinyl leukotrienes) and reduces production of proinflammatory cytokines, including IL-5. IL-5 is produced by several types of cells, including T_H2 lymphocytes and type 2 innate lymphoid cells (ILC2), and by activated mast cells. IL-5 has protean effects on eosinophil poesis, maturation in the bone marrow, emigration into the circulation, migration to sites of inflammation, and activation to produce oxidative damage and toxic eosinophil granule protein release. Mepolizumab and reslizumab reduce the activity of IL-5 at all these sites and reduce eosinophilic inflammatory responses. Individually and collectively, airway inflammation, airway hyperresponsiveness, and bronchoconstriction may produce structural airway changes of increased smooth muscle mass, thickened lamina reticularis, and mucus gland hypertrophy, collectively known as airway wall remodeling. It has not been proven than that any asthma therapy reduces or eliminates airway wall remodeling.

approved in the United States for patients with severe asthma and peripheral eosinophilia.[11] Mepolizumab reduces the rate of exacerbations by almost 50%; the need for oral corticosteroids is also reduced by 50%, with little effect on lung function.[26,27] No specific level of peripheral blood eosinophilia is listed in the package insert, but the referenced clinical trials required at least 150 eosinophils/μL. This level of eosinophilia has not been prospectively assessed as a predictive biomarker of therapeutic response. Mepolizumab is administered by injection every 4 weeks, at a standard dose of 100 mg subcutaneously.

Reslizumab is administered every 4 weeks by intravenous infusion, using weight-based dosing (3 mg/kg). Reslizumab reduces the rate of exacerbations by about 50%, reduces symptoms, and improves FEV_1 by 110 mL.[28,29] Clinical trials referenced in the package insert required at least 400 eosinophils/μL for entry, but this requirement has not been validated as a predictive biomarker. Both mepolizumab and reslizumab reduce biologic activity of IL-5 in the pathogenesis of eosinophilic inflammation (Figure 4).

Oral steroids are an effective option for uncontrolled disease and for asthma exacerbations but have significant adverse effects, including glucose intolerance, weight gain, and salt and water retention, if used continuously (Table 2).

Special Considerations

Consultation with an asthma specialist is warranted for patients who are at step 4 or higher in the US guideline[13] or who have a life-threatening exacerbation, poor responsiveness to prescribed treatment, occupational triggers, atypical presentation, need for more than 2 bursts of oral corticosteroids, or who need specialized testing for allergies, lung function, or bronchoscopy.[12,13] Asthma may present with symptoms predominantly in association with exercise. The timing of symptoms is generally within a few minutes of cessation of exercise and is termed "exercise induced bronchospasm." Pretreatment with albuterol 15 minutes prior to anticipated exercise can minimize or eliminate these symptoms.[12,13] Management of comorbid conditions (allergic rhinitis, sinusitis, gastroesophageal reflux, obstructive sleep apnea) improves asthma control.[12,13] Adding exercise as a component of lifestyle change in overweight patients with asthma appears to improve asthma control.[71]

Selected Current Controversies

All long-acting β_2-agonists marketed in the United States carry a black box warning for increased risk of death and serious adverse events, based primarily on results from a large observational study with important limitations in study design.[72] More recent evidence

suggests that the appropriate use of long-acting β_2-agonists in combination with inhaled steroids is not associated with increased serious adverse events.[69] Additional well-controlled studies may clarify this matter.

All biologic agents marketed in the United States require parenteral administration and are costly ($15 000-$30 000 annually). Omalizumab and reslizumab carry black box warnings for the risk of anaphylaxis, and their use is generally limited to asthma specialists. No data are available regarding direct comparisons of these agents, the optimal duration of therapy, or whether combinations of biologics are superior to individual treatments.[11]

Bronchial thermoplasty, a procedure approved in 2010 for severe asthma, delivers radiofrequency energy to the airway. The mechanisms by which this procedure affects the pathogenesis of asthma remain unclear; changes in adaptive immunity and airway smooth muscle have been suggested but not proven.[73] Reduced exacerbations (50%) and emergency department visits (85%) are seen for at least 1 year after treatment.[74] Trials of up to 5 years were not rigorously controlled, so evidence for long-term benefit is limited.[30] The GINA,[13] but not the NAEPP,[12] specify a role for bronchial thermoplasty. The American Thoracic Society and European Respiratory Society have recommended that bronchial thermoplasty be conducted within the context of a clinical trial or registry.[75]

Prognosis

Asthma continues to be an important cause of morbidity and some mortality in the United States (Table 1). Rates of asthma mortality are particularly elevated among non-Hispanic African American patients (25.4 per million per year) compared with white patients (8.8 per million per year).[2]

Controller agents appear not to modify the natural history of asthma.[12,13] Patients with persistent disease should be counseled that treatment for an extended period will likely be necessary. In patients with mild-moderate asthma whose disease is controlled with a daily regimen of low-medium dose of inhaled corticosteroids, the administration of these agents only at the time that short-acting β_2-agonists are used for relief of symptoms provides control not different from that achieved with daily inhaled corticosteroids, using a reduced dose of inhaled corticosteroids; however, this approach has not yet been incorporated into formal guidelines.[76]

Accelerated loss of lung function is seen in some, but not all, patients with asthma.[77] Loss of lung function is principally observed in patients in whom exacerbations are frequent (2% predicted greater annual loss of FEV_1 in patients with exacerbation compared with those without),[78] highlighting the potential importance of preventing exacerbations. However, no long-term controlled trials having trajectory of lung function as the primary outcome have been published, so the effects of guideline-based treatment on loss of lung function remain unclear.

Conclusions

Asthma is characterized by variable airway obstruction, airway hyperresponsiveness, and airway inflammation. Management of persistent asthma requires avoidance of aggravating environmental factors, availability of short-acting β_2-agonists for rapid relief of symptoms, and daily use of inhaled corticosteroids. Other controller medications, such as long-acting bronchodilators and biologics, may be required in moderate and severe asthma. Patients with severe asthma generally benefit from consultation with an asthma specialist for consideration of additional treatment, including injectable biologic agents.

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