

Asthma

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KEYWORDS

- Asthma • Airway inflammation • Allergens • Genetic risk
- Asthma symptoms • Asthma diagnosis • Asthma management
- Hyperresponsiveness

Asthma is a common, chronic disorder of the airways, but it is a complex disorder. Asthma is characterized by:

1. Variable and recurring symptoms
2. Airflow obstruction
3. Bronchial hyperresponsiveness
4. Underlying inflammation.

The comorbid conditions of allergic rhinitis and asthma have been well documented, are frequently observed, and may represent a spectrum of the same disease entity (1-airway hypothesis).^{1,2} Health care providers managing allergic rhinitis need to be comfortable with their ability to recognize and treat asthma and inflammation of the lower airway.

The clinical presentation of asthma can be highly variable over time and is often dependent on several factors:

- The inflammation of asthma in the airway of susceptible individuals causes recurrent episodes of wheezing, breathlessness, chest tightness, and coughing, which often worsen at night and in the early morning
- Episodes of inflammation are usually associated with widespread, but often variable, airflow obstruction that is frequently reversible
- This inflammation can also cause an increase in the existing bronchial hyperresponsiveness typical of asthma.

The interaction of these features of asthma determines the clinical manifestations and severity of asthma and the response to treatment.

The relationship between the upper and lower airway inflammation should not be underestimated. Rhinitis occurs in 75% to 90% of adult subjects with allergic asthma and 80% of those with nonallergic asthma.³ The incidence of asthma is high in developed nations, constituting the most common chronic disease of childhood, affecting more than 7 million children in the United States.⁴ Allergic disease is associated with the development, severity, and persistence of asthma. As an example, up to 80% of

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children with atopic dermatitis develop asthma and/or allergic rhinitis later in childhood.⁵ Conversely, asthma occurs in 25% to 50% of individuals with rhinitis. Adults with perennial rhinitis are more likely to have asthma than those without rhinitis.⁶ The odds of developing asthma are eightfold higher in patients with allergic rhinitis and almost 12-fold higher in patients with nonallergic rhinitis.

PATHOPHYSIOLOGY OF ASTHMA

The immunohistopathologic features of asthma include an inflammatory cell infiltration into the respiratory tract. Neutrophils, eosinophils, lymphocytes, mast cell activation, and epithelial cell injury are common cellular findings. In some patients with progression of disease, persistent changes in airway structure occur, including subbasement fibrosis, mucus hypersecretion, injury to epithelial cells, smooth muscle hypertrophy, and angiogenesis. Numerous inflammatory mediators have also been implicated in the inflammatory process, and management of these mediators has held some promise in the progression and management of the reactive process of asthma. Chemokines, cytokines, cysteinyl-leukotrienes, nitric oxide, and immunoglobulin E (IgE) all play a role in the development of airway inflammation.⁷⁻¹⁰

Central to the variable clinical presentations of asthma is the presence of underlying airway inflammation, which is also varied over time within the same individual and among individuals. This inflammatory variability has distinct, but overlapping, patterns that reflect different aspects of the clinical presentation of the disease, such as intermittent versus persistent asthma or acute versus chronic manifestations.

Acute symptoms of asthma usually arise from bronchospasm and require and respond to bronchodilator therapy. Acute and chronic inflammation can affect not only the airway caliber and airflow but also underlying bronchial hyperresponsiveness, which enhances susceptibility to bronchospasm.¹¹

RISK FACTORS FOR ASTHMA

The variables that result in the initiation of the inflammatory process in some individuals are being investigated. Although no definitive pattern exists, there is evidence that the origin of the airway inflammation occurs early. The expression of the clinical presentation of asthma is complex and involves interaction between genetic host factors and environmental exposures occurring at a critical time in the development of the immune system. The development of asthma likely results from complex interactions between multiple genetic and environmental influences (**Box 1**).¹² The onset of asthma for most patients begins early in life, with the pattern of disease persistence determined by early, recognizable risk factors including atopic disease, recurrent wheezing, and a parental history of asthma.

Box 1
Variables influencing the development of asthma

- Innate Immunity
- Genetics
- Sex
- Allergens/type and timing of exposure
- Respiratory infections
- Environmental exposures

The genetic predisposition for the development of an IgE-mediated response to common aeroallergens is the strongest identifiable predisposing factor for developing asthma. The Third National Health and Nutrition Examination Survey (NHANES) found that one-half of asthma cases were attributable to atopy.¹³

Additional precipitating events may be important variables for exacerbation of asthma and may also contribute to the development of asthma. These events include viral respiratory infections, exposure to environmental tobacco smoke, and obesity (Fig. 1).^{14–16}

NATURAL HISTORY OF ASTHMA

Persistence and severity of asthma seems to involve a progression of airway inflammation resulting in airway remodeling and eventual irreversible airway obstruction. An important question is whether antiinflammatory medication (ie, inhaled corticosteroids [ICS]) given early in the course of disease might interrupt this process and prevent permanent declines in lung function, or whether the progression to more persistent and severe disease is predetermined by other variables.

Early studies have indicated that, although current treatments are effective in controlling symptoms, reducing airflow limitations, and preventing exacerbations, present treatments for persistent disease (eg, ICS) do not seem to prevent the underlying severity of asthma from progressing,¹⁷ which suggests that currently available therapy controls, but does not modify, the underlying disease process.

In the pediatric population, age 3 years or younger, patients most at risk for developing progressive disease were most likely to have had 4 or more episodes of

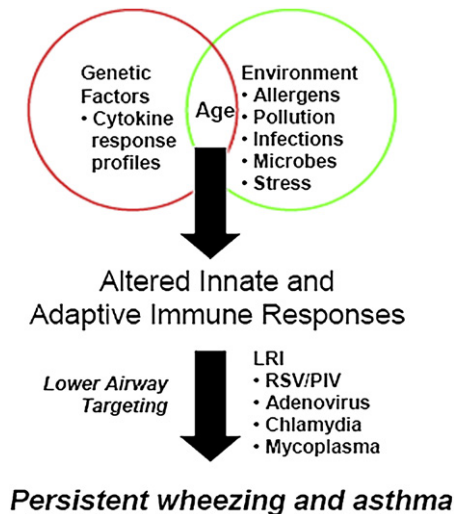


Fig. 1. Host factors and environmental exposures. Guideline for the diagnosis and management of asthma. (From National Asthma Education and Prevention Program: Expert Panel Report III: guidelines for the diagnosis and management of asthma. Bethesda (MD): National Heart, Lung, and Blood Institute; 2007. [NIH publication no. 08-4051]. Available at: www.nhlbi.nih.gov/guidelines/asthma/asthgdln.htm. Accessed on September 01, 2007.)

wheezing during the previous year, and either a parental history of asthma, a diagnosis of atopic dermatitis, or evidence of sensitization to aeroallergens.¹⁷

Data on adult onset asthma are inconclusive on the ability of ICS to alter progression of disease, but seem promising. In 2 long-term observational studies, an association was noted between ICS therapy and reduced decline in forced expiratory volume in 1 second (FEV₁) in adults who had asthma.^{18,19}

If ICS can change the natural course of asthma, some continued improvement in lung function might be expected once ICS are discontinued. The best available evidence in children aged 5 to 12 years²⁰ and aged 2 to 3 years¹⁷ showed that, although ICS provide superior control and prevention of symptoms and exacerbations during treatment, symptoms and airway hyperresponsiveness worsen when treatment is withdrawn. This evidence suggests that currently available therapy controls, but does not modify, the underlying disease process.

Asthma Management: Assessment and Monitoring

Key elements of assessment and monitoring include evaluation of severity of symptoms, control of symptoms, and responsiveness to therapy. Severity, defined as the intrinsic intensity of the disease process, can often be easily measured and should be assessed when the patient is not receiving long-term control therapy. Controls of symptoms are defined as the degree to which the clinical manifestations of asthma can be minimized. Assessment of symptoms, functional impairment, and risks of future events should be minimized. Responsiveness is defined as the ease with which asthma control is achieved.

The diagnosis of asthma is the initial step in reducing the symptoms, functional limitations, impairment in quality of life, and risk of adverse future events that accompany the disease. The ultimate goal of treatment is to enable patients to live with none of the manifestations of asthma.

The initial assessment of the severity of the disease allows for an estimate of the type and intensity of treatment needed. Responsiveness to asthma treatment is variable; therefore, to achieve the goals of therapy, follow-up assessment must be made and treatment should be adjusted accordingly. Patients who have asthma that is well controlled at the time of a clinical assessment should be monitored over time, as the processes of asthma can vary in intensity, and treatment should be adjusted accordingly.

HISTORICAL INFORMATION

Some patients with asthma report or present with the classic triad of symptoms: wheeze, cough (typically worsening at night), and shortness of breath or difficulty breathing. Wheezing does not have a standard meaning for patients and may be used by those without a medical background to describe a variety of sounds. Cough may be dry or productive. Other patients have only 1 or 2 of these symptoms. Some patients describe chest tightness or a bandlike constriction. In contrast, chest pain is uncommonly used to describe the sensation of asthma.

Because the symptoms of asthma are also seen in a myriad of other respiratory diseases, it may be difficult to be certain of the diagnosis of asthma based on history alone.^{21–23} However, certain historical features heighten the prior probability of asthma:

- Episodic symptoms: asthmatic symptoms characteristically come and go, resolving spontaneously with removal from the triggering stimulus or in response to antiasthmatic medications. Patients with asthma also may remain asymptomatic for long periods of time

- Characteristic triggers of asthma include exercise, cold air, and exposure to allergens. Similarly, viral infections are common triggers for asthma, although they can trigger exacerbations in other chronic respiratory conditions as well. A strong family history of asthma and allergies or a personal history of atopic diseases (specifically, atopic dermatitis, seasonal allergic rhinitis and conjunctivitis, or hives) favors a diagnosis of asthma in a patient with suggestive symptoms.

Physical Findings

Widespread, high-pitched, musical wheezes are characteristic of asthma, although these findings are not specific and are often absent between exacerbations of the disease. Wheezes are heard most commonly on expiration, but can also occur during inspiration. The presence or absence of wheezing on physical examination is a poor predictor of the severity of airflow obstruction in asthma. Wheezing may be heard in patients with mild, moderate, or severe airway narrowing, whereas widespread airway narrowing may be present in individuals without wheezing. Thus, the presence of wheezing suggests the likely presence of airway narrowing, but not its severity.

PULMONARY FUNCTION TESTING

Variability of patient symptoms and disease exacerbations has resulted in pulmonary function testing becoming a critical tool in the diagnosis and management of asthma. Measurement of peak expiratory flow rate and spirometry are used most frequently.

Peak Expiratory Flow Rate

The peak expiratory flow rate (PEFR) is the measure of airflow during a brief, forceful exhalation. The measurement of peak flow rates can be taught to the patient and routinely used at home to monitor disease severity. As with most pulmonary function testing, the resulting measurements are highly dependent on the patient's expiratory effort and technique. Thus, it is important that the clinician assesses and monitors the patient's technique and effort level and corrects any mistakes. The PEFR maneuver can be performed sitting or standing. Proper technique involves taking a maximally large breath in, putting the peak flow meter quickly to the mouth and sealing the lips around the mouthpiece, and blowing as hard and fast as possible into the meter. For PEFR, the effort does not need to be sustained beyond 1 to 2 seconds. The patient should perform the maneuver 3 times and record the highest of the 3 measurements. Patients should perform the test routinely 2 to 3 times per day and keep a log, establishing a personal-best PEFR. PEFRs may be misleading and mild airflow obstruction may be present when the peak flow remains within the normal range. Reduced peak flow measurements do not differentiate between obstructive and restrictive diseases; spirometry and sometimes measurement of lung volumes are necessary to distinguish the two. Peak flow measurements are not sufficient to distinguish upper airway obstruction (eg, vocal cord dysfunction) from asthma. The validity of PEFR measurements depends on patient effort and technique. There is also no standardization among peak flow measurements. Despite the shortcomings, many patients use PEFR to successfully follow the progression of their asthmatic disease.

Spirometry

Spirometry, which includes measurement of FEV₁ and forced vital capacity (FVC), provides valuable information that is useful in the diagnosis of asthma. Spirometry is a simple office procedure that can be completed in 10 to 15 minutes with virtually

no risk to the patient. The test is dependent on patient effort, although standard protocols and normative values have been established.

Spirometry can be used to determine normal from abnormal lung function and can categorize the abnormalities into obstructive or restrictive patterns. Spirometry can also be used to characterize the severity of the asthma and can be used to assess the reversibility of the obstructive abnormality if the testing is repeated after administration of a bronchodilator.

Variable airflow obstruction is the hallmark of asthma. An atopic patient with a cough, shortness of breath, and/or wheezing who has expiratory airflow obstruction pattern on spirometry that reverses to normal with treatment almost certainly has asthma. In contrast, the person with cough and chest congestion who has consistently normal spirometry probably does not have asthma, and alternative explanations (eg, recurrent bronchitis) should be sought.

An obstructive pattern on spirometry is identified numerically by a reduction in the ratio of FEV_1 to the FVC. When FEV_1/FVC is reduced to less than normal (best defined by 95% confidence intervals around the normal values, information that is provided electronically by modern computerized spirometers), airflow obstruction is present. When the FEV_1/FVC ratio is normal or increased, there is no expiratory airflow obstruction.

Having identified the presence of airflow obstruction by a reduction in FEV_1/FVC , the severity of airflow obstruction is then categorized by the degree of reduction of the FEV_1 less than normal. By convention, the severity of airflow obstruction based on spirometry is graded as mild, moderate, severe, and very severe based on the reduction in FEV_1 . These categories are used for pulmonary function interpretation and are not the same as categories used to stage asthma severity.

Bronchodilator Response

The ability to acutely reverse airflow obstruction is tested by administering 2 to 4 puffs of a quick-acting bronchodilator (albuterol) and repeating spirometry 10 to 15 minutes later. The variability of the measurement is such that an increase of less than 12% may occur simply because of making repeated measurements. However, an increase in FEV_1 of 12% or more, accompanied by an absolute increase in FEV_1 of at least 200 mL, can be attributed to bronchodilator responsiveness with 95% certainty (**Fig. 2**).

Occasionally, patients with asthma have airflow obstruction on spirometry, but fail to exhibit a 12% or greater increase in FEV_1 following bronchodilator (a false-negative response). There are several reasons for false-negative response to a bronchodilator:

- Incomplete inhalation of the bronchodilator caused by using the metered-dose inhaler incorrectly
- Recent use of a bronchodilator resulting in near-maximal bronchodilation before testing
- Minimal airflow obstruction at the time of testing (FEV_1 already close to 100%)
- In some patients with asthma, the presence of irreversible airways obstruction caused by chronic airways inflammation or scarring (so-called airway remodeling).

Bronchoprovocation Testing

Bronchoprovocation testing is another tool for diagnosing asthma. Bronchoprovocation is used to attempt to provoke airflow obstruction using a stimulus known to elicit airway narrowing. Patients with asthma are more sensitive to such stimuli than are

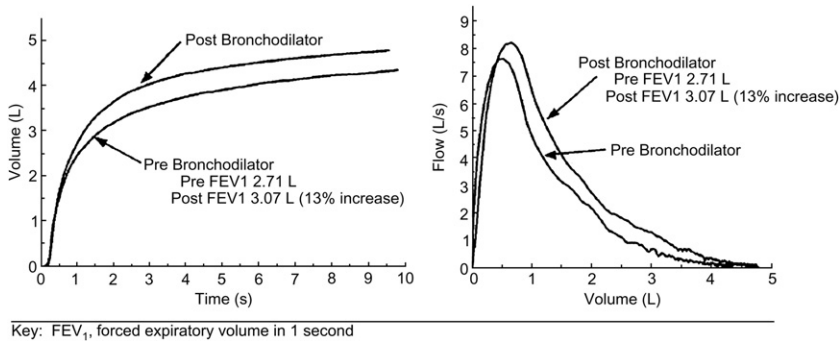


Fig. 2. Sample spirometry: volume time and flow volume curves. (From National Asthma Education and Prevention Program: Expert Panel Report III: guidelines for the diagnosis and management of asthma. Bethesda (MD): National Heart, Lung, and Blood Institute; 2007. [NIH publication no. 08-4051]. Available at: www.nhlbi.nih.gov/guidelines/asthma/asthgdln.htm. Accessed on September 01, 2007.)

patients without asthma. Methacholine, exercise, hyperventilation of cold dry air, and inhaled histamine have all been used to provoke bronchoconstriction.

PATIENT MONITORING/PATIENT EDUCATION

Effective asthma management requires a proactive, preventive approach. Routine follow-up visits for patients with asthma are recommended, at a frequency of every 1 to 6 months, depending on the severity of symptoms and patients' responsiveness to therapy. Signs and symptoms of active disease and pulmonary function testing should be reviewed regularly. Quality-of-life questions, number of exacerbations, adherence with treatment, medication side effects, satisfaction with care, and expectations of therapy should all be discussed.

Symptom Assessment

Symptoms over the past 2 to 4 weeks should be assessed at each visit. Assessment should address daytime symptoms, nighttime symptoms, use of short-acting inhaled β -agonists to relieve symptoms, and difficulty in performing normal activities and exercise. There are several validated questionnaires that are easy for patients to complete.^{24–30} An example is the Asthma Control Test (<http://www.asthmacontrol.com>).

The following questions are representative:

Assessment of impairment

- Has your asthma awakened you at night or in the early morning?
- Have you needed your quick-acting relief medication more than usual?
- Have you needed any unscheduled care for your asthma, including calling in, an office visit, or going to the emergency room?
- Have you been able to participate in school/work and recreational activities as desired?
- If you are measuring your peak flow, has it been lower than your personal best?
- Have you had any side effects from your asthma medications?

Assessment of risk

- Have you needed any unscheduled care for your asthma, including calling in, an office visit, or going to the emergency room?
- Have you taken any oral glucocorticoids for your asthma?

Well-controlled asthma is characterized by daytime symptoms no more than twice per week and nighttime symptoms no more than twice per month. Short-acting β -agonists for relief of asthma symptoms should be needed less often than twice weekly, and there should be no interference with normal activity (preventive use of a short-acting β -agonist, such as before exercise, is acceptable even if used in this way on a daily basis). Peak flow should remain normal or near normal. Oral glucocorticoid courses and/or urgent-care visits should be needed no more than once per year.³¹

Environmental Controls/Controlling Triggers

The identification and avoidance of asthma triggers is a critical component of successful asthma management, and successful avoidance or remediation may reduce the patient's need for medications. Directed questions can identify specific triggers and contributing conditions.

Adults should be questioned about symptoms not only in the home but also in the workplace, because asthma can be exacerbated by both irritant and allergen exposures in occupational settings. Some triggers are unavoidable, such as upper respiratory tract illnesses, exercise, hormonal fluctuations, and extreme emotion, and patients should be taught to adjust their management accordingly.

Allergen provocation of asthma is common and the patient should be questioned about symptoms triggered by common inhaled allergens. Indoor allergens, such as dust mites, animal dander, molds, and cockroaches, are of particular importance as triggers of asthma. If the history suggests that the patient has allergic triggers, basic avoidance measures should be advised, and further evaluation, including specific allergen testing via in vitro or skin testing techniques, is warranted.

Inhaled irritants as a trigger of asthma are also common and include tobacco smoke, wood smoke from stoves or fireplaces, strong perfumes and odors, chlorine-based cleaning products, and air pollutants. These exposures should always be considered when discussing environmental controls.

Patients should be cognizant of avoiding irritants, and avoid exertion outdoors on days when levels of air pollution are increased.

Clinicians should be vigilant for comorbid conditions in patients with poorly controlled asthma. In adults, these conditions include chronic obstructive pulmonary disease (COPD)/emphysema, allergic bronchopulmonary aspergillosis, gastroesophageal reflux, obesity, obstructive sleep apnea, rhinitis/sinusitis, vocal cord dysfunction, and depression/chronic stress. In young children, contributing conditions include respiratory syncytial virus infection, foreign body aspiration, bronchopulmonary dysplasia, cystic fibrosis, and obesity.³²

Medication reactions also need to be considered when discussing the control of asthma triggers. Nonselective β -blockers can trigger severe asthmatic attacks, even in the small amounts absorbed systemically from topical ophthalmic solutions. Selective β -1 blockers have also been shown to aggravate asthma in some patients, especially at higher doses.

Aspirin and nonsteroidal antiinflammatory drugs can trigger asthma symptoms in approximately 3% to 5% of adult asthmatic patients. The incidence of aspirin-exacerbated respiratory disease is higher among asthmatic patients with nasal polyposis (constituting triad asthma or Samter triad). Aspirin-sensitive asthma is uncommon in children.

Annual administration of influenza vaccine is recommended for patients with asthma because they are at risk for complications of infection. However, vaccination does not reduce the number or severity of asthma exacerbations during the influenza season, and providers should ensure that patients understand this distinction.

Administration of pneumococcal vaccination is recommended for adults whose asthma is severe enough to require controller medication and for children with asthma who require chronic oral glucocorticoid therapy.³³

Dietary sulfites (used in foods to prevent discoloration) have been shown to provoke asthma. As many as 5% of patients with asthma may note significant and reproducible exacerbations following ingestion of sulfite-treated foods and beverages, such as beer, wine, processed potatoes, dried fruit, sauerkraut, or shrimp.

PHARMACOLOGIC TREATMENT

Pharmacologic treatment is the mainstay of management in most patients with asthma. The 2007 National Asthma Education and Prevention Program (NAEPP) Expert Panel Report presented a stepwise approach to pharmacologic therapy, which is reflected in this review.³²

These guidelines are well written and are intended to support, as opposed to dictate, care. Allowing for treatment is based on the clinician's clinical judgment.

The stepwise approach to pharmacotherapy is based on increasing medications until asthma is controlled, and decreasing medications, when possible, to minimize side effects. Decisions regarding the patient's management should be discussed at every visit. The initial step in determining appropriate therapy for patients who have not been treated with a controller medication is classifying the severity of the patient's asthma.

Categories of Asthma Severity

Asthma severity is determined by considering the following 3 factors³²:

1. Reported symptoms over the previous 2 to 4 weeks
2. Current level of lung function (FEV₁ and FEV₁/FVC values)
3. Number of exacerbations requiring oral glucocorticoids per year

The use of these 3 elements to determine severity in adolescents more than 12 years of age and in adults is presented in **Table 1**.

The classification of severity in children aged 5 to 11 years is similar to that in adults (**Table 2**).

However, severity in children less than 4 years of age is classified differently (**Table 3**).

The classification for children older than 12 years of age to adults divides asthma severity into intermittent or persistent based on frequency of symptoms. Persistent asthma is further classified into mild, moderate, or severe depending on symptom severity and objective testing.

Intermittent Asthma

The criteria for adolescents and adults diagnosed with intermittent asthma are:

- Daytime asthma symptoms occurring 2 or fewer days per week
- Two or fewer nocturnal awakenings per month
- Use of short-acting β -agonists to relieve symptoms fewer than 2 times a week
- No interference with normal activities between exacerbations
- FEV₁ measurements between exacerbations are consistently within the normal range (ie, equal to 80% of predicted normal)
- Only 1 or no exacerbations of symptoms requiring oral glucocorticoids per year.

Table 1
The 3 elements used to determine asthma severity in adolescents older than 12 years and in adults

		Classification of Asthma Severity (Youths ≥12 y of Age and Adults)			
Components of Severity		Intermittent	Persistent		
			Mild	Moderate	Severe
Impairment	Symptoms	≤2 d/wk	>2 d/wk but not daily	Daily	Throughout the day
Normal FEV ₁ /FVC:	Nighttime awakenings	≤2x/mo	3–4/mo	>1/wk but not nightly	Often 7/wk
8–19 y 85%	Short-acting β ₂ -agonist	≤2 d/wk	>2 d/wk but not >1/d	Daily	Several times per day
20–39 y 80%	use for symptom control				
40–59 y 75%	(not prevention of EIB)				
60–80 y 70%	Interference with normal activity	None	Minor limitation	Some limitation	Extremely limit
	Lung function	Normal FEV ₁ between exacerbations			
		FEV ₁ >80% predicted	FEV ₁ ≥80% predicted	FEV ₁ >60% but <80% predicted	• FEV ₁ <60% predicted
		FEV ₁ /FVC normal	FEV ₁ /FVC normal	FEV ₁ /FVC reduced 5%	• FEV ₁ /FVC reduced >5%
Risk	Exacerbations	0–1/y (see note)	≥2/y (see note) 		
	requiring oral	← Consider severity and interval since last exacerbation. Frequency and severity may fluctuate over time for			
	systemic	patients in any severity category. →			
	corticosteroids	Relative annual risk of exacerbations may be related to FEV ₁			

Abbreviation: EIB, exercise-induced bronchospasm.

From National Asthma Education and Prevention Program: Expert Panel Report III: guidelines for the diagnosis and management of asthma. Bethesda (MD): National Heart, Lung, and Blood Institute; 2007. [NIH publication no. 08-4051]. Available at: www.nhlbi.nih.gov/guidelines/asthma/asthgdln.htm. Accessed on September 01, 2007.

Table 2
The classification of severity in children aged 5 to 11 years

Components of Control		Classification of Asthma Control (Children 5–11 y of Age)		
		Well Controlled	Not Well Controlled	Very Poorly Controlled
Impairment	Symptoms	≤2 d/wk but not more than once on each day	>2 d/wk or multiple times on ≤2 d/wk	Throughout the day
	Nighttime awakenings	≤1/mo	≥2/mo	≥2/wk
	Interference with normal activity	None	Some limitation	Extremely limited
	Short-acting β_2 -agonist use for symptom control (not prevention of EIB)	≤2 d/wk	>2 d/wk	Several times per day
	Lung function			
	• FEV ₁ or peak flow	>80% predicted/personal best	60%–80% predicted/personal best	<60% predicted/personal best
	• FEV ₁ /FVC	>80%	75%–80%	<75%
Risk	Exacerbations requiring oral systemic corticosteroids	0–1/y	≥2/y (see note)	
	Reduction in lung growth	Consider severity and interval since last exacerbation	Evaluation requires long-term follow-up	
	Treatment-related adverse effects	Medication side effects can vary in intensity from none to very troublesome and worrisome. The level of intensity does not correlate to specific levels of control but should be considered in the overall assessment of risk		

Abbreviation: EIB, exercise-induced bronchospasm.

From National Asthma Education and Prevention Program: Expert Panel Report III: guidelines for the diagnosis and management of asthma. Bethesda (MD): National Heart, Lung, and Blood Institute; 2007. [NIH publication no. 08-4051]. Available at: www.nhlbi.nih.gov/guidelines/asthma/asthgdln.htm. Accessed on September 01, 2007.

Table 3
Severity in children less than 4 years of age

		Classification of Asthma Control (Children 0–4 y of Age)		
	Components of Control	Well Controlled	Not Well Controlled	Very Poorly Controlled
Impairment	Symptoms	≤2 d/wk	>2 d/wk	Throughout the day
	Nighttime awakenings	≤1/mo	>1/mo	>1/wk
	Interference with normal activity	None	Some limitation	Extremely limited
	Short-acting β_2 -agonist use for symptom control (not prevention of EIB)	≤2 d/wk	>2 d/wk	Several times per day
Risk	Exacerbations requiring oral systemic corticosteroids	0–1/y	2–3/y	>3/y
	Treatment-related adverse effects	Medication side effects can vary in intensity from none to very troublesome and worrisome. The level of intensity does not correlate to specific levels of control but should be considered in the overall assessment of risk		

From National Asthma Education and Prevention Program: Expert Panel Report III: guidelines for the diagnosis and management of asthma. Bethesda (MD): National Heart, Lung, and Blood Institute; 2007. [NIH publication no. 08-4051]. Available at: www.nhlbi.nih.gov/guidelines/asthma/asthgdln.htm. Accessed on September 01, 2007.

If these various elements are discordant, the patient's asthma should be categorized at the level of the most severe.

In addition, a person using a short-acting β -agonist to prevent exercise-induced asthmatic symptoms might fit into this category even if exercising more than twice per week. Others in whom asthmatic symptoms arise only in certain infrequently occurring circumstances (eg, on encountering a cat or during viral respiratory tract infections) are also considered to have intermittent asthma.

Mild Persistent Asthma

Mild persistent asthma is characterized by:

- Symptoms occurring more than twice weekly (although < daily)
- Between 3 and 4 nocturnal awakenings per month caused by asthma
- Need to use short-acting β -agonists to relieve symptoms more than 2 times a week (but not daily)
- Minor interference with normal activities
- FEV₁ measurements within normal range (equal to 80% of predicted normal) and the FEV₁/FVC ratio is normal (based on age-adjusted values)
- Two or more exacerbations requiring oral glucocorticoids per year.

If the various elements are discordant, the patient's asthma should be categorized at the level of the most severe.

Moderate Persistent Asthma

The presence of any of the following is considered an indication of moderate disease severity classified as moderate persistent asthma:

- Daily symptoms of asthma
- Nocturnal awakenings more than once per week
- Daily need for short-acting β -agonists for symptom relief
- Some limitation in normal activity
- Spirometry in mild persistent asthmatics shows an FEV₁ between 60% and 80% of predicted and the FEV₁/FVC ratio is reduced to less than normal (based on age-adjusted values)
- Two or more exacerbations annually requiring oral glucocorticoids.

Severe Persistent Asthma

Patients with severe persistent asthma experience 1 or more of the following symptoms of asthma:

- Symptoms of asthma throughout the day
- Nocturnal awakenings nightly
- Need for short-acting β -agonists for symptom relief several times per day
- Extreme limitation in normal activity
- Objective pulmonary function testing reveals FEV₁ less than 60% of predicted and an FEV₁/FVC reduced to less than normal (based on age-adjusted values).

These patients require oral glucocorticoids 2 or more times per year.

PHARMACOTHERAPY FOR ASTHMA

Initiating Therapy in Previously Untreated Patients

The initiation of asthma therapy in a stable patient who is not already receiving medications is based on the severity of the individual's asthma. A stepwise treatment approach has been developed in children younger than 15 years of age to adults (Fig. 3), children aged 5 to 15 years (Fig. 4), and in children younger than 4 years of age. These guidelines are offered in an attempt to facilitate rapid control of symptoms with the least amount of medications required. Increasing or reducing therapy, as symptoms dictate, reflects the variable nature of asthma.³²

Intermittent (Step 1)

Patients with mild intermittent asthma are best treated with a quick-acting inhaled β_2 -selective adrenergic agonist, taken as needed for relief of symptoms (see Fig. 3).³⁴ Patients for whom triggering of asthmatic symptoms can be predicted (eg, exercise-induced bronchoconstriction) are encouraged to use their inhaled β -agonist approximately 10 minutes before exposure to prevent the onset of symptoms.

Mild Persistent (Step 2)

The distinction between intermittent and mild persistent asthma is important, because current guidelines for mild persistent asthma call for initiation of daily long-term controller medication. For mild persistent asthma, the preferred long-term controller is a low-dose inhaled glucocorticoid (see Fig. 3). Regular use of inhaled glucocorticoids reduces the frequency of symptoms (and the need for short-acting β -agonists

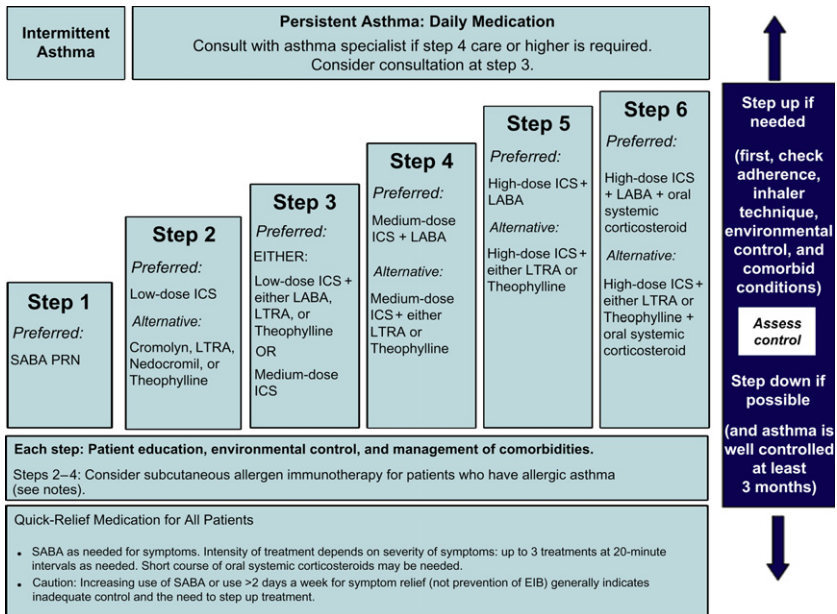


Fig. 3. Stepwise approach for managing asthma in children 5 to 11 years of age. (From National Asthma Education and Prevention Program: Expert Panel Report III: guidelines for the diagnosis and management of asthma. Bethesda (MD): National Lung, and Blood Institute; 2007. [NIH publication no. 08-4051]. Available at: www.nhlbi.nih.gov/guidelines/asthma/asthgdln.htm. Accessed on September 01, 2007.)

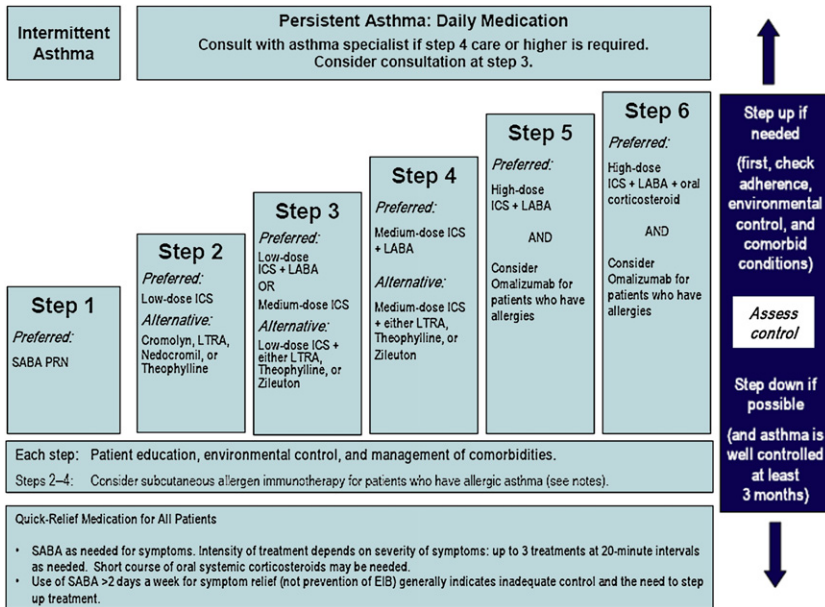


Fig. 4. Stepwise approach for managing asthma in youths more than 12 years of age and adults. (From National Asthma Education and Prevention Program: Expert Panel Report III: guidelines for the diagnosis and management of asthma. Bethesda (MD): National Heart, Lung, and Blood Institute; 2007. [NIH publication no. 08-4051]. Available at: www.nhlbi.nih.gov/guidelines/asthma/asthgdln.htm. Accessed on September 01, 2007.)

for symptom relief), improves the overall quality of life, and decreases the risk of serious exacerbations.^{35–37} Regular use of inhaled glucocorticoids has not been shown to definitively prevent progressive loss of lung function over time.

Alternative strategies for treatment of mild persistent asthma include leukotriene receptor antagonists, theophylline, and cromoglycates (see **Fig. 3**). Patients receiving long-term controller therapy should continue to use their short-acting β -agonist as needed for relief of symptoms and before exposure to known triggers of their symptoms.

Moderate Persistent (Step 3)

For moderate persistent asthma, the preferred therapies are either low doses of an inhaled glucocorticoid plus a long-acting inhaled β -agonist, or medium doses of an inhaled glucocorticoid (see **Fig. 3**). The former combination has proved more effective in controlling asthmatic symptoms than increasing the dose of inhaled glucocorticoids, although it entails the potential risk of adverse outcomes that have been reported in association with long-acting inhaled β -agonists.^{38,39}

Alternative strategies include adding a leukotriene modifier (leukotriene receptor antagonist or lipoxygenase inhibitor) or theophylline to low-dose inhaled glucocorticoids.

Severe Persistent (Step 4 or 5)

For severe persistent asthma, the preferred treatments are medium (step 4) or high (step 5) doses of an inhaled glucocorticoid, in combination with a long-acting inhaled β -agonist (see **Fig. 3**).

In addition, for patients who are inadequately controlled on high-dose inhaled glucocorticoids and long-acting β -agonists, the anti-IgE therapy omalizumab may be considered if there is objective evidence (allergy skin tests or in vitro measurements of allergen-specific IgE) of sensitivity to a perennial allergen and if the serum IgE level is within the established target range.

Step 6 Therapy

For severe asthma not controlled through step 5, step 6 involves the addition of oral glucocorticoids on a daily or alternate-day basis.

Assessing Control to Adjust Therapy

Assessment of the level of control, rather than severity of classification, of disease is used to adjust therapy in returning patients. Assessing level of control also is useful to alter therapy in patients evaluated for the first time while already taking a long-term controller medication. Control is assessed based on the level of impairment/symptoms over the past 2 to 4 weeks and through using current FEV₁ or peak flow measurements. Estimates of risk for worsening of symptoms based on history or a validated questionnaire is also a useful tool.³²

The clinician should determine whether the patient's asthma is well controlled or not using the information gathered. If the asthma is well controlled, therapy can be continued or possibly reduced to minimize medication side effects. If the asthma is not well controlled, therapy should be increased. Therapy should be readjusted at each visit, because of the inherent variability of asthma. The management of asthma is a dynamic process that changes in accordance with the patient's needs over time. Educating the patient with respect to the nature of the disease and the control process facilitates management.

Efficacy of Asthma Management

A prospective, randomized trial applied the management recommendations of previous NAEP guidelines to approximately 1500 patients with a variety of severities of asthma for a period of 12 months.⁴⁰ The use of guideline-based management resulted in significant improvement in health-related quality of life in most patients, regardless of disease severity. In this study, subjects who required inhaled glucocorticoids were randomly assigned to receive either fluticasone propionate (FP) alone or the combination of FP and salmeterol (S). Subjects were evaluated every 3 months and medications were stepped up as needed. With both treatments, more than one-half of patients achieved well-controlled or totally controlled asthma, although control was slightly better with FP plus S. The greatest improvements occurred in the first few months of therapy. Thus, the stepwise approach to asthma management is effective in reducing symptoms and improving health-related quality of life. The current guidelines have expanded on this same basic approach.³²

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