

# Pediatric Asthma in a Nutshell

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## Practice Gap

Asthma affects the health and quality of life of many children and is a major cause of emergency department visits and hospital admissions. Advances in clinical and basic research have not led to a significant reduction in urgent care visits. One probable contributor is the lack of universal implementation of asthma guidelines into clinical practice.

## Objectives After completing this article, readers should be able to:

1. Identify the key clinical features of asthma and distinguish different asthma phenotypes.
2. Differentiate asthma from other conditions that cause wheezing and cough.
3. Accurately assess asthma severity and level of control and develop a comprehensive treatment plan.
4. Identify commonly used asthma medications, their mechanism of action, and their adverse effect profile.
5. Identify barriers to good asthma control and how to remove them.

## INTRODUCTION

The estimated cost of caring for children with asthma between 2005 and 2009 was approximately \$10.7 billion. (1) For children younger than 5 years, almost half of the cost was for inpatient care, one-third for medications, and one-tenth for outpatient care. In contrast, for children between ages 6 and 17 years, only 5% was spent on inpatient care and most for medications and outpatient visits. These numbers demonstrate the high burden of asthma and illustrate that young children are most vulnerable to exacerbations that require hospital care. Despite the high expense, the numbers of emergency department visits and hospital admissions for children with asthma have not significantly decreased. The lack of improvement in the burden of asthma is likely due to multiple factors, including inadequate implementation of existing guidelines. (2) According to a report from the National Center for Health Statistics, only one-third of patients with asthma had a written asthma action plan, and one-third did not receive education on early warnings signs of an asthma exacerbation and appropriate response. The chronic nature of the disease adds additional challenges, including the need for

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### ABBREVIATIONS

ICS      inhaled corticosteroid  
LABA    long-acting inhaled  $\beta_2$ -agonist  
SABA    short-acting  $\beta_2$ -agonist

longitudinal care, financial burden to families, apprehensions about adverse effects, and disease fatigue. In addition, it can be difficult to accurately diagnose asthma in children who experience first episodes of wheezing, and evaluation and treatment algorithms are complex. The goals of this review are to summarize key facts about pediatric asthma and to present management strategies that will help in the care of children with the disease.

## EPIDEMIOLOGY

Asthma is a common chronic disease with significant variations in prevalence among countries, states, cities, and neighborhoods. (3) The exact cause of the differences in prevalence is not entirely clear but likely represents variances in genetics, socioeconomic factors, and external environmental and in utero exposures to toxins (eg, air pollution or tobacco smoke exposure) that contribute either directly to airway inflammation and irritation or indirectly through the modulation of lung-specific or systemic immune responses. One theory, the hygiene hypothesis, postulates that exposure to bacteria and endotoxin at a young age influences the development of the immune system and has a resulting protective effect against the development of asthma. On the other hand, a clean environment that minimizes exposures at a young age is thought to push the immune system toward a more allergic phenotype with an increased risk of the development of asthma.

## DEFINITION AND PATHOGENESIS

Asthma is not a singular disease but a symptom complex with a variety of different clinical phenotypes that can present in an acute, chronic, or acute on chronic pattern. It is defined as a disease of the airways with inflammation, constriction of airway smooth muscles, mucous production, and edema that lead to obstruction and air trapping. The clinical symptoms of asthma are cough, wheezing, chest tightness, prolonged exhalation, and/or shortness of breath.

When the airways of patients with asthma are exposed to environmental triggers, they respond with exaggerated bronchoconstriction, a phenomenon that is commonly described as airway hyperresponsiveness. A strict definition requires a formal challenge with pulmonary function testing before and after challenge with methacholine or another airway irritant or allergen. In clinical practice, the term is often used to describe the development of clinical symptoms of airway inflammation and constriction (wheezing, cough, or shortness of breath) in response to external triggers. Bronchial hyperresponsiveness increases with late-phase asthmatic responses to allergen exposure and with viral respiratory

infections. The response pattern to an IgE-mediated allergen challenge is of clinical importance because it leads to immediate obstruction, which resolves and is followed in 4 to 12 hours by persistent late-phase obstruction.

## TRIGGERS

Viral respiratory tract infections are a major trigger for asthma exacerbations in a large number of patients, which explains the seasonal increase in asthma exacerbations during the winter months. (4) Infants with symptomatic bronchiolitis due to respiratory syncytial virus or rhinovirus are at increased risk for wheezing in the first few years of life. It is not yet clear whether an infection with these viruses at a young age sets children up for a lifelong increased risk of airway inflammation and asthma or whether these viruses are a marker for underlying asthma. Other common triggers for asthma exacerbations are exercise, weather changes, and exposure to tobacco or other smoke, air pollution and smog, cold or hot air, strong perfumes, or other irritants. Children who are atopic are especially susceptible to environmental allergens, and a small subgroup of children have asthma that is triggered by drugs such as aspirin (approximately 5%) or  $\beta$ -adrenergic blocking agents. These drugs should therefore be used cautiously, especially in children with severe and poorly controlled asthma.

## CLINICAL ASPECTS

The challenge in diagnosing asthma is that there is no simple test to confirm the diagnosis when most patients first present. The symptoms of coughing and wheezing are not specific for asthma but rather represent a response of the respiratory system and lungs to a variety of underlying harmful stimuli. The wheezing due to allergic or viral-induced inflammation sounds similar. Respiratory viruses, such as rhinovirus, respiratory syncytial virus, and many others, can cause wheezing irrespective of an underlying diagnosis of asthma, even in the healthy host. Furthermore, epidemiologic studies of asthma have found that wheezing is a common symptom in preschool children and that most of these children will not develop chronic persistent asthma.

On the basis of epidemiologic studies, an Asthma Predictive Index was developed to improve the accuracy of a diagnosis of asthma in children younger than 3 years. (5) Those who had 3 or more episodes of wheezing per year and met at least 1 major criterion (eczema or parental asthma) or at least 2 minor criteria (allergic rhinitis, wheezing unrelated to colds, or blood eosinophil count  $>4\%$ ) are at significantly higher risk of having asthma symptoms later in life. Children with wheezing episodes that do not meet

the criteria for a positive Asthma Predictive Index result are not likely to develop chronic asthma symptoms.

### PULMONARY FUNCTION TESTING

The most commonly used method to measure airflow obstruction is spirometry. It measures the volume and speed of flow of forcibly exhaled air. (6) Data from the test help to establish a baseline, to support the diagnosis and assess the severity of airflow obstruction, responsiveness to albuterol, and response to changes in the treatment regimen or clinical course. The pattern of the flow volume loops provides information about fixed or dynamic airway obstruction. It is not unusual for a child to require a few practice sessions to get reliable and reproducible results. A normal spirometry result does not necessarily rule out asthma, especially if the patient has an intermittent asthma phenotype. Children diagnosed as having asthma should undergo initial spirometry at approximately age 6 years followed by testing at least every 1 to 2 years or more frequently if asthma is poorly controlled or treatment is being changed. Once a baseline has been established, these values can be used as a reference during future visits and facilitate the detection of improvements or worsening in lung function, which in turn can result in the stepping up or down of asthma therapies.

### PEAK FLOW METERS

Although the routine use of peak flow meters is not recommended, measurement of peak flow can be helpful in patients who have poor perception of their asthma symptoms and severity. Peak flow establishes a baseline to which they can compare daily measurements, facilitating earlier detection of any decline in lung function, with resulting adjustment in maintenance therapy or initiation of oral corticosteroid treatment. Tracking peak flow can also be beneficial when adjusting long-term maintenance therapy because the patient will be able to see improvements in peak flow with new therapies.

### ALLERGY TESTING

Testing for allergies with either skin testing or blood-based assays can detect previously unknown triggers or confirm suspected triggers. Most asthmatic school-age children have positive immediate-type allergy skin test results. It is important to interpret the results in the clinical context. For example, if a skin test result is negative for cat extract but playing with a cat elicits coughing and wheezing at home, the clinical observation cannot be discounted and needs to be taken into consideration.

### DIFFERENTIAL DIAGNOSIS

Asthma is a common respiratory disease, and most children with a history of recurrent or persistent wheezing and typical risk factors have asthma. However, it is important to be mindful of conditions that mimic asthma or contribute to symptoms that are difficult to control. Whenever a patient does not respond to standard asthma therapy or has respiratory symptoms that are difficult to control, an alternative diagnosis should be explored (Table 1). A thorough history can be helpful in narrowing the list of possible suspects. A family history of chronic lung disease other than asthma can provide important clues. Wet and productive cough is frequently present in children with chronic bronchiectasis. These children should undergo chest radiography and sweat chloride testing to rule out cystic fibrosis (a negative newborn screening test result does not rule out cystic fibrosis because the result occasionally can be falsely negative). Lower than normal body mass index from birth or a declining body mass index points toward a systemic underlying disease. The sudden onset of symptoms with persistence of cough and wheeze may indicate foreign-body aspiration. Coughing and choking with feedings, with subsequent chest congestion or wheezing, are suggestive of dysphagia and aspiration. A history of more than 2 pneumonias raises the possibility of an underlying immunodeficiency.

### VOCAL CORD DYSFUNCTION

A fairly common but frequently overlooked diagnosis that can mimic asthma is vocal cord dysfunction. (7) Vocal cord dysfunction is defined as an involuntary closure of the vocal cords that typically occurs during exercise. It can occur in isolation or concomitantly with asthma. Postnasal drip and gastroesophageal reflux can contribute to vocal cord irritation in some patients but are not the only causes. The typical patient is a teenager with a competitive personality who excels in academics and sports. Often, the patients will have a fairly sudden onset of shortness of breath with exercise that resolves quickly. Patients with vocal cord dysfunction generally do not experience symptoms of shortness of breath unrelated to exercise and do not have symptoms during sleep. Standard asthma therapies, such as inhaled corticosteroids (ICSs), leukotriene inhibitors, or short-acting  $\beta_2$ -agonists (SABAs), usually provide little or no relief. Patients will often describe difficulties breathing in rather than breathing out as with asthma. When asked an open-ended question such as, "Can you please show me with your hand where the air is getting blocked?" they will frequently point right at their lower neck as opposed to their chest. During examination, an inspiratory stridor can often be heard loudest

TABLE 1. Asthma Differential Diagnosis

RED FLAG	POSSIBLE DIAGNOSIS
Sudden onset of symptoms	Foreign body
Coughing and choking when eating or drinking	Oropharyngeal dysphagia with aspiration
Poor growth and low body mass index	Cystic fibrosis, immunodeficiency
Family history of sterile males	Cystic fibrosis, immotile cilia syndrome.
Chronic rhinorrhea and recurrent sinus infections	Cystic fibrosis, immotile cilia syndrome
Acute onset without history of asthma in teenager	Vocal cord dysfunction
Chronic wet productive cough	Bronchiectasis
More than 2 episodes of pneumonia	Immunodeficiency

over the larynx. Abnormal spirometry can support the diagnosis of vocal cord dysfunction. The typical flow-volume curve shows a truncated inspiratory loop and normal expiratory loop, indicating dynamic airflow obstruction (Figure 1). Flexible laryngoscopy confirms the diagnosis when abnormal vocal cord movement is observed during a symptomatic episode and rules out other laryngeal disorders. Patients with an atypical picture benefit from formal exercise testing with or without direct laryngoscopy during the study to rule out exercise-induced asthma, deconditioning, or a cardiac condition. Patients with vocal cord dysfunction respond well to targeted breathing and relaxation exercises with a speech therapist who is experienced in treating the condition. Treatment of vocal cord dysfunction in patients with comorbid asthma entails teaching the patient to distinguish between an asthma attack that requires short-term treatment with a SABA

and a vocal cord dysfunction attack to minimize the risk of unnecessary pharmacotherapy.

### EXERCISE-INDUCED ASTHMA

Shortness of breath along with coughing or wheezing during physical exertion can be a symptom of poorly controlled asthma. (8) However, some patients experience symptoms associated with bronchoconstriction only with exercise and otherwise have no history consistent with asthma. Symptoms typically start within a few minutes of initiation of vigorous exercise and subside within 20 to 30 minutes, although they can last up to 90 minutes when left untreated. Most episodes of exercise-induced asthma are self-limited, but rare cases of severe attacks and even death have been reported. It is important to assess all patients with

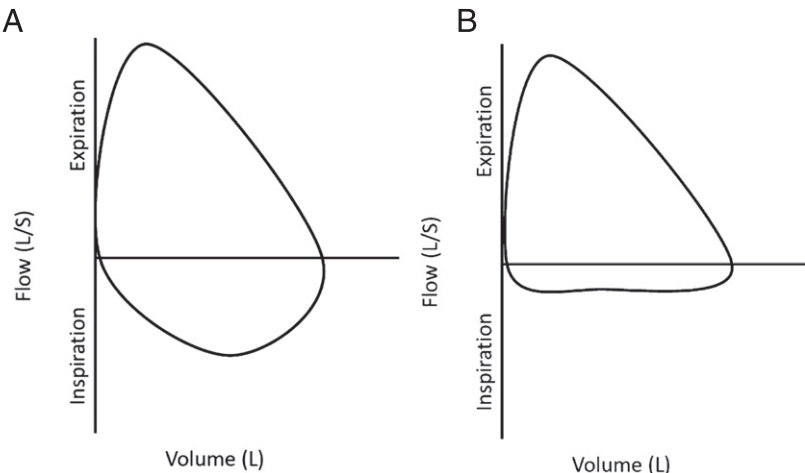


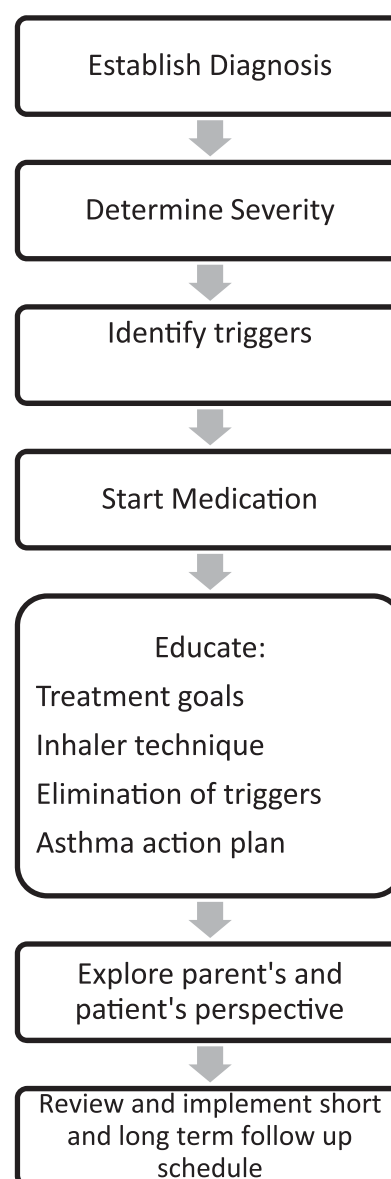
Figure 1. Flow volume loop changes in vocal cord dysfunction. A. Normal flow volume loop. B. Truncation of inspiratory loop, indicating dynamic airflow obstruction.

A: normal flow-volume loop. B: truncation of inspiratory loop, indicating dynamic airflow obstruction.

asthma for symptoms related to vigorous physical activity because it is an informal challenge test that brings out symptoms in patients who are asymptomatic when sedentary. The gold standard for the diagnosis of exercise-induced asthma is a greater than 10% decrease in forced expiratory volume at 1 second compared with preexercise level. Spirometry can help determine the severity of exercise-induced bronchospasm. Depending on the age and cognitive ability of the child, it might be difficult or impossible to obtain spirometry data, and the diagnosis is then largely based on the clinical presentation and response to therapy. Certain environmental factors, such as cold or dry air, chlorine from a swimming pool, or air pollution and smog, can exacerbate exercise-induced asthma. Patients should be encouraged to start off with gradual warm-up exercises before more vigorous activity. Premedication 15 minutes before exercise with a SABA is typically the first-line therapy. If premedication does not sufficiently alleviate asthma symptoms or if the patient needs it more than once per day, the addition of a controller medication (inhaled steroid or leukotriene inhibitor) is recommended. If the patient still has poor control of exercise-induced symptoms, a mast cell-stabilizing agent could be considered before exercise. Long-acting  $\beta_2$ -agonists (LABAs) are not recommended as single-agent therapy because of concerns that they may mask underlying airway inflammation and increase the risk of severe sudden respiratory deterioration.

## MANAGEMENT

Once asthma has been established as a likely diagnosis, it is important to determine its severity (Figure 2). The current recommendation is to take impairment and risk into consideration when determining the optimal initial therapeutic approach. Impairment refers to the frequency and severity of asthma symptoms, objective measurements with pulmonary function testing (spirometry is most accurate with peak flow as the adjunct measurement), and their effect on a patient's life. Asthma impairment is categorized as intermittent or persistent with mild, moderate, or severe expression. Risk refers to a history of asthma and includes the frequency and speed of deterioration, severity of exacerbations, ability to access urgent care, and need for oral systemic steroids. Assessment of risk is essential for patients with intermittent symptoms or exacerbations because some of them will have rare but life-threatening exacerbations. (9) The National Asthma Education and Prevention Program guidelines provide age-based criteria for impairment and risk and suggestions for initial therapy in correspondence with 6 steps of escalating drug therapy (Table 2 and Table 3). Anti-inflammatory drugs are the mainstay of therapy for patients with mild, moderate, or severe persistent



**Figure 2.** Initial evaluation for asthma. Adapted with modification from the National Asthma Education and Prevention Program. *Asthma Care Quick Reference Guide: Diagnosing and Managing Asthma*. Bethesda, MD: National Heart, Lung, and Blood Institute; 2012. NIH publication 12-5075.

asthma and patients with intermittent asthma with increased risk. After initiation of therapy, the goals are to reduce impairment (control asthma symptoms, decrease need for SABAs, improve lung function, and maintain no activity limitations) and risk (prevention of exacerbations and reduction and ideally elimination of emergency department care and hospital admissions). Current asthma guidelines serve as a general framework, and treatment needs to be carefully tailored to best benefit the individual patient. The initial evaluation should conclude with a review of proper drug administration and a patient-specific asthma action plan. Most children will do

TABLE 2. **Assessment of Asthma Severity and Initial Therapy**

VARIABLE	INTERMITTENT	MILD	MODERATE	SEVERE
Impairment				
Symptom frequency	≤2 days per week	>2 days per week but not daily	Daily	Throughout day
Nighttime awakenings	Age 0-4 years: 0 Age 5 years to adult: ≤2 times per month	Age 0-4 years: 1-2 times per month Age 5 years to adult: 3-4 times per month	Age 0-4 years: 3-4 times per month Age 5 years to adult: >1 times per week but not nightly	Age 0-4 years: >1 time per week Age 5 years to adult: >7 times per week
Interference with activity	None	Minor limitation	Some limitation	Extremely limited
SABA use (except for EIB)	≤2 days per week	Age 0-4 years: >2 days per week, not daily Age 5 years to adult: >2 days per week, not daily and not more than once per day	Daily	Several times per day
FEV <sub>1</sub> , % predicted	>80%	>80%	60-80%	<60%
Risk				
Asthma exacerbations that require oral steroids	0-1 per year	Age 0-4 years: ≥2 in 6 months or wheezing >4 times per year lasting >1 day and risk factors for persistent asthma Age 5 years to adult: ≥2 per year	More frequent and intense events indicate greater severity	More frequent and intense events indicate greater severity
Treatment				
Initial treatment steps <sup>a</sup>	Step 1	Step 2	Age 0-4 years and ≥12 years: step 3 Age 5-11 years: medium-dose inhaled corticosteroid option	Age 0-4 years: step 3 Age 5-11 years: medium-dose inhaled corticosteroid option or step 4 Age ≥12 years: step 4 or 5

EIB=exercise-induced bronchospasm; FEV<sub>1</sub>=forced expiratory volume in 1 second; SABA=short-acting  $\beta_2$ -agonist.

Adapted from the National Asthma Education and Prevention Program. Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma, 2007. Bethesda, MD: National Heart, Lung, and Blood Institute; 2007. NIH publication 07-4051.

<sup>a</sup>See Table 3 for an explanation of the treatment steps.

well with a metered-dose inhaler and a spacer. Spacers come in a variety of age-appropriate sizes and can be used starting in infancy. Parents often prefer an inhaler and spacer because drug delivery through this setup is much quicker than administration via a compressor with nebulizer. However, some children are intolerant of a spacer and do better with a nebulizer. The elimination of environmental triggers should be emphasized, and the parents and patient should have the opportunity to express their perspectives and any concerns about the diagnosis or medication adverse effects.

Asthma care can only be successful if a long-term relationship is established among the parents, patient, and asthma care team. Regularly scheduled follow-up visits are especially

important for patients with more severe impairment and those at high risk. At each follow-up visit, asthma control should be assessed, environmental triggers identified, treatment stepped up or down, inhaler technique reviewed, concerns addressed, and goals set (Figure 3 and Table 4). Asthma questionnaires, such as the Asthma Control Test, Asthma Therapy Assessment Questionnaire, or Asthma Control Questionnaire, are tools that help standardize assessment for control. The follow-up schedule should be tailored to the individual patient and adjusted based on impairment, risk, and need for additional education. Most patients should be seen at least every 6 months, at intervals of 2 to 6 weeks while gaining control and every 3 months if step down in therapy is anticipated.

TABLE 3. **Stepwise Approach for Asthma Therapy: Preferred Treatment**

AGE, Y	STEP 1	STEP 2	STEP 3	STEP 4	STEP 5	STEP 6
0-4	SABA as needed	Low-dose ICS	Medium-dose ICS	Medium-dose ICS and LABA or montelukast	High-dose ICS and LABA or montelukast	High-dose ICS and LABA or montelukast and oral corticosteroids
5-11	SABA as needed	Low-dose ICS	Low-dose ICS and LABA, LTRA, or theophylline or medium-dose ICS	Medium dose ICS and LABA	High-dose ICS and LABA	High-dose ICS and LABA and oral corticosteroids
≥12	SABA as needed	Low-dose ICS	Low-dose ICS and LABA or medium-dose ICS	Medium-dose ICS and LABA	High-dose ICS and LABA Consider omalizumab for allergic patients	High-dose ICS and LABA and oral corticosteroids Consider omalizumab for allergic patients

ICS=inhaled corticosteroid; LABA=long-acting inhaled  $\beta_2$ -agonist; LTRA=leukotriene antagonist; SABA=short-acting  $\beta_2$ -agonist.

Adapted from the National Asthma Education and Prevention Program. Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma, 2007. Bethesda, MD: National Heart, Lung, and Blood Institute; 2007. NIH publication 07-4051.

## PATIENT EDUCATION

A collaborative and trusting relationship between the family and the medical professionals is critical for successful long-term management of the disease. Families that have a child with asthma need to learn how to correctly give daily maintenance medication and how to detect and respond appropriately to fluctuations in asthma control, knowing

when to seek professional help and when to go to the emergency department. It is unfortunately not uncommon for parents to never fill prescribed ICS prescriptions out of fear of adverse effects or because the goals of therapy were not clearly explained. Parents and patients that understand the goals of therapy and rationale for choosing specific medications are more likely to actively participate in long-

**Figure 3.** Follow-up visit. Adapted with modification from the National Asthma Education and Prevention Program. *Asthma Care Quick Reference Guide: Diagnosing and Managing Asthma*. Bethesda, MD: National Heart, Lung, and Blood Institute; 2012. NIH publication 12-5075.

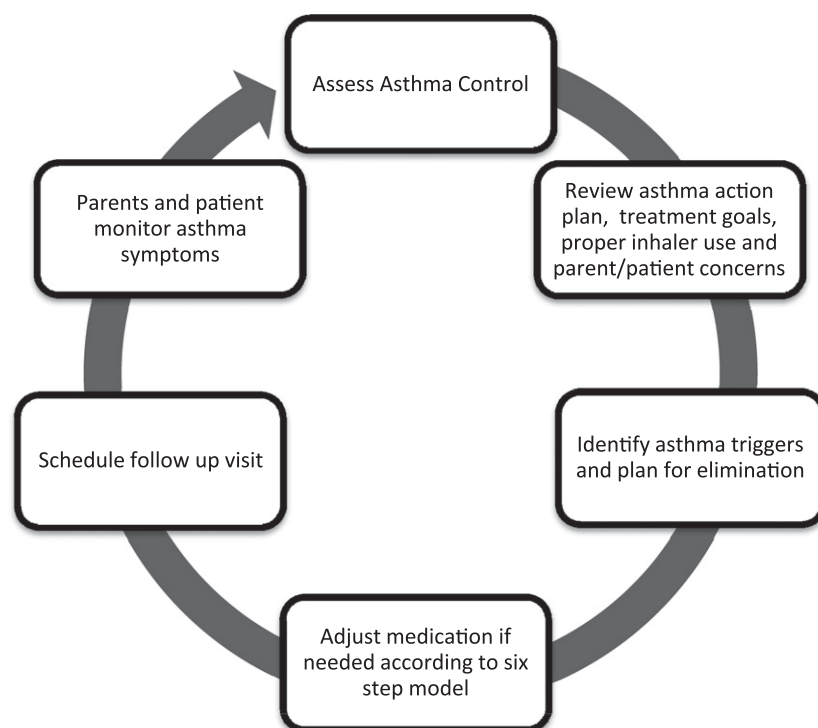




TABLE 4. **Assessment of Asthma Control**

VARIABLE	WELL CONTROLLED	NOT WELL CONTROLLED	VERY POORLY CONTROLLED
Impairment			
Symptom frequency	Age 0-4 years and $\geq 12$ years: $\leq 2$ days per week Age 5-11 years: $\leq 2$ days per week, not more than once per day	Age 0-4 years and $\geq 12$ years: $> 2$ days per week Age 5-11 years: $> 2$ days per week or multiple times on $\leq 2$ days per week	Throughout day
Nighttime awakenings	Age 0-11 years: $< 1$ time per month $\geq 12$ years: $\leq 2$ times per month	Age 0-4 years: $> 1$ time per month Age 5-11 years: $\geq 2$ times per month Age $\geq 12$ years: 1-3 times per week	Age 0-4 years: $\geq 1$ time per week Age 5-11 years: $\geq 2$ times per week Age $\geq 12$ years: $\geq 4$ times per week
Interference with activity	None	Some limitation	Extremely limited
SABA use (except for EIB)	$\leq 2$ days per week	$> 2$ days per week	Several times per day
FEV <sub>1</sub> , % predicted	$> 80\%$	60-80%	$< 60\%$
Risk			
Asthma exacerbations that require systemic corticosteroids	0-1 time per year	Age 0-4 years: 2-3 times per year Age 5 years to adult: $\geq 2$ times per year	Age 0-4 years: $> 3$ times per year Age 5 years to adult: $\geq 2$ times per year
Action			
Recommended action	Maintain current step	Age 0-4 years and $\geq 12$ years: go up 1 step Age 5-11 years: go up at least 1 step	Consider short course of oral steroids Step up 1-2 steps

EIB=exercise-induced bronchospasm; FEV<sub>1</sub>=forced expiratory volume in 1 second; SABA=short-acting  $\beta_2$ -agonist.

Adapted from the National Asthma Education and Prevention Program. Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma, 2007. Bethesda, MD: National Heart, Lung, and Blood Institute; 2007. NIH publication 07-4051.

term care. Therefore, the goals of asthma therapy should be reviewed with the family, and any concerns or reservations about the plan should be reviewed and addressed. Education should include the review of asthma triggers and how to avoid them. Signs and symptoms that indicate suboptimal or poor asthma control should be reviewed.

## ASTHMA ACTION PLAN

An asthma action plan provides written care instructions to the family that are personalized to the patient's asthma type. A well-designed plan serves as both an educational and treatment tool. Many versions are available. The choice of plan should be based on whether it is age appropriate for the child, at a reading level that allows comprehension by the family, and ideally in language spoken in the family's home. It should include contact information for the pediatrician, a list of medications, and instructions clarifying which medication is being used for maintenance or rescue therapy. Parents should be taught how to assess work of

breathing and how to look for prolonged exhalation and intercostal or supraclavicular retractions. Warning signs of a severe asthma exacerbation, such as increased work of breathing, inability to feed or speak in sentences, color change, irritability, or lethargy, should be discussed. Parents and patients should have the opportunity to review the plan with their medical professional or asthma educator and to ask questions for clarification. The plan is most useful when posted or kept in an easily accessible place. Additional copies for school or other family members ensure that instructions are available in case of an asthma exacerbation or if control is starting to slowly slip. The plan should be reviewed and updated at each follow-up visit for asthma.

For examples of action plans see the following: asthma action plans in English, Spanish, Chinese, and Vietnamese (<http://www.rampasthma.org/info-resources/asthma-action-plans/>) and MaineHealth ([http://www.mainehealth.org/mh\\_body.cfm?id=363#track](http://www.mainehealth.org/mh_body.cfm?id=363#track)), which contains links to clinical tools, including asthma control tests, asthma action plans, the Pediatric Asthma Toolkit, links to clinical guidelines



flipchart, inhaler and peak flow instructions, and an asthma symptom and peak flow diary.

## **$\beta_2$ -AGONISTS**

One of the hallmarks of asthma is bronchoconstriction due to contraction of smooth muscle fibers that surround the conducting airways. (10)  $\beta_2$ -Agonists relieve constriction by binding to specific receptors on airway smooth muscle cells, triggering a signaling cascade that leads to the relaxation of airway muscles and improved airflow.

$\beta_2$ -Agonists can be divided by their pharmacologic characteristics into SABAs and LABAs. The SABAs, such as albuterol, have a rapid onset (within 15 minutes) and a relatively short duration of action of approximately 3 to 4 hours. In contrast, the effect of a LABA can last up to 12 hours. Use of LABAs alone for the treatment of asthma is not recommended because of concerns that the prolonged bronchodilator effect can mask airway inflammation and put the patient at risk for sudden and life-threatening asthma exacerbations. There is evidence in adults that the addition of a LABA to an ICS improves asthma control and lung function. For children and especially young children, the evidence for this practice is not as clear, and combinations of an ICS and a LABA should therefore be used cautiously in that group with close follow-up.

Inhaled  $\beta_2$ -agonists have the benefit of acting locally in the airways of the lung with a decreased risk of adverse effects. However, receptors for drugs are not only present in lung tissue and when larger amounts of the drug are given but also reach the systemic circulation via absorption through the airway epithelium or gastrointestinal system when the drug gets swallowed. Potential adverse effects from  $\beta_2$ -agonists include agitation, irritability, tremor, insomnia, tachycardia, arrhythmia, and agitation. Hypokalemia secondary to shift of potassium into the skeletal muscle can occur with higher doses. Patients with diabetes mellitus are at risk for hyperglycemia due to stimulation of hepatic glycogenolysis. The frequency of  $\beta_2$ -adrenergic drug use should be assessed at each clinic visit because frequent use indicates poor asthma control and excessive daily use has been associated with increased mortality and with diminished symptom control.

## **INHALED CORTICOSTEROIDS**

Inhaled corticosteroids are the most commonly prescribed maintenance therapy for asthma. (11) They effectively decrease airway inflammation, decrease bronchial hyper-responsiveness, relieve asthma symptoms, and improve

lung function, exerting their effect through a number of pathways, including the regulation of gene expression. They form a complex with the glucocorticoid receptor in the cellular cytoplasm, which then moves to the cell nucleus, where it binds to specific DNA sequences and either inhibits or facilitates transcription of RNA. The complex also interacts with other transcription factors and exerts direct non-genomic effects. The net effect of this is a suppression of inflammation. The broad mechanism of action explains why corticosteroids are still the most effective anti-inflammatory drug for the treatment of asthma. It also explains why corticosteroids are effective in treating the late-phase response to allergen exposure but not the immediate response.

Most children with asthma present before age 5 years and are treated with ICSs. The need for therapy at a young age raises concerns for adverse effects related to growth and development. Studies in patients who require low to medium doses of corticosteroids have found a slight slowing in growth in some patients, typically occurring at the time of initiation of therapy, with no notable differences in final height. However, studies indicate that patients who require high-dose ICSs are at increased risk of adverse effects, including slowing in growth and adrenal suppression. The incidence and severity of such adverse effects vary and are complicated by the fact that poorly controlled asthma is a risk factor for poor growth. To minimize the risk of adverse effects, it is important to eliminate or minimize triggers that contribute to airway inflammation and the need for ICSs. In addition, medication should be administered to limit systemic exposure. A spacer should be used with a metered-dose inhaler, and the patient should be encouraged to rinse the mouth after taking the medication to decrease oral deposition and absorption of the drug and to decrease the risk of oral thrush, one of the more common adverse effects of ICSs. If the patient is getting the ICS via nebulizer and facemask, the skin should be cleaned with a wet cloth afterward to decrease skin exposure. Most importantly, patients should periodically be assessed for readiness to step down the ICS dose or to stop taking steroids.

## **LEUKOTRIENE ANTAGONISTS**

Leukotriene antagonists are attractive as a therapy for asthma because they block inflammatory pathways that are active in the disease. They are relatively easy to administer orally as opposed to inhaled medications, which are more prone to administration error. A number of different leukotriene antagonists have been developed. The most commonly used in children younger than 12 years is montelukast. It blocks the cysteinyl leukotriene 1 receptor on airway epithelial cells, airway smooth muscle, vascular

endothelial cells, eosinophils, and neutrophils. It is usually well tolerated, and some parents and patients prefer it as an initial controller medication because it does not carry the risks associated with ICSs. Montelukast is frequently used as an add-on therapy in addition to ICSs and can be beneficial in patients with comorbid allergic rhinitis, young children with recurrent viral-induced exacerbations, or children with exercise-induced symptoms.

## TREATMENT OF ASTHMA EXACERBATIONS

Treatment of asthma exacerbations should take into consideration the pattern of a patient's previous attacks because exacerbations occur in a variety of patterns. Some patients experience a slow increase in asthma symptoms (wheezing, cough, and chest tightness) for days or weeks, whereas others experience a rapid progression from the onset of symptoms to severe shortness of breath within hours. Patients who have a history of rapid progression from the onset of an exacerbation to severe respiratory distress are at high risk of hospital admission and life-threatening asthma attacks. The threshold for starting systemic corticosteroid therapy in these patients should therefore be relatively low.

Children who exhibit symptoms consistent with bronchospasm (cough, wheezing, chest tightness, or retractions) should initially receive treatment with a SABA. Up to 2 to 3 treatments can be given back to back 20 minutes apart. If the patient has persistent wheezing and chest tightness after the treatments, systemic corticosteroid therapy should be started and the patient evaluated as soon as possible by a physician. If  $\beta_2$ -agonist treatment leads to resolution of symptoms after the initial dose, it can be given as needed up to every 4 hours. If the patient needs a  $\beta_2$ -agonist every 4 hours for repeated doses, oral corticosteroids should be considered because they will treat the underlying inflammation, improve adrenergic response (sensitization, upregulation, and increase of  $\beta_2$ -receptors), and improve forced expiratory volume in 1 second and oxygenation.

A subgroup of children is at increased risk for life-threatening asthma exacerbations. These children require meticulous and regular follow-up care and a well-developed action plan for acute exacerbations. Factors that increase risk include history of life-threatening exacerbation with intensive care unit admission and/or need for mechanical ventilation, lack of perception of asthma symptoms, poor adherence, psychiatric or psychological comorbidities, poor baseline asthma control with daily symptoms and/or reduced pulmonary function, daily use of oral corticosteroids, excessive use of SABAs, use of LABAs, and dysfunctional social environment.

## EVALUATION OF EXACERBATION SEVERITY

A number of different scores have been developed to improve the accuracy of grading disease severity. They take into account the presence of wheezing, work of breathing, duration of exhalation, retractions, air entry, oxygen saturation as measured by pulse oximetry, respiratory rate, and accessory muscle use. The more commonly used scores are the Pediatric Asthma Severity Score and the Pediatric Respiratory Assessment Measure. A simplified score that comprises 3 clinical parameters, the RAD score (Respiratory rate; Accessory muscle use; Decreased breath sounds), has recently been proposed. (12) Warning signs of a severe exacerbation are lethargy, pallor or cyanosis, severe retractions, prolonged exhalation, inability to speak, poor air movement (in severe cases airflow so poor that no wheezing is generated), and, if the patient is able to perform the maneuver, peak flow rate less than 40 predicted. (13) Patients who exhibit these symptoms require immediate transfer to a pediatric emergency department. They should be given supplemental oxygen and an SABA until arrival of an ambulance.

Chest radiography is not usually indicated in the management of a typical asthma attack. However, if the clinical presentation is atypical with severe symptoms, the lung examination reveals marked discrepancies between sides, a foreign body is suspected, or concerns about a pneumothorax exist, chest radiography can be helpful. It is not uncommon to find some atelectasis on the chest radiograph of a patient with asthma due to increased mucous production and airway inflammation. The presence of atelectasis usually does not require bronchoscopy, antibiotics, or chest physical therapy.

## PROGNOSIS

Asthma is not a singular disease but a symptom complex with a variety of different clinical phenotypes; the prognosis and clinical course are variable. Some patients experience an improvement or resolution of asthma symptoms as they progress through puberty, whereas others experience persistence or worsening. Children with early-onset asthma (age <3 years) who have a parental history of asthma, a confirmed diagnosis of atopic dermatitis, or sensitization to aeroallergens are least likely to outgrow asthma. Furthermore, even asymptomatic patients with normal lung function are at risk of future asthma flare-ups, depending on environmental factors, such as viral infections, workplace or home airway allergens, and irritants or pollutants.

## Summary

- On the basis of strong research evidence, (1) asthma is a leading cause of emergency department visits and hospital admissions for children.
- On the basis of research evidence, (2) implementation of asthma guidelines by medical professionals is not optimal.
- On the basis of research evidence, (5) the Asthma Predictive Index supports a diagnosis of chronic asthma in children younger than 3 years.
- On the basis of strong research evidence, (8) premedication with a short-acting  $\beta_2$ -agonist is the preferred initial therapy for exercise-induced asthma.
- On the basis of strong research evidence, (9) anti-inflammatory therapy with inhaled corticosteroids is an effective treatment for asthma.
- On the basis of research and consensus, (9) assessment of impairment and risk followed by scheduled assessment for asthma control is recommended.
- On the basis of research and consensus, (9) the establishment of a close cooperative relationship among medical professionals, patients with asthma, and their families is an important component of asthma management.

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## Asthma in a Nutshell

Holger Link, MD



## PIR Quiz

1. Which of the following meets the criteria for a diagnosis of asthma in children younger than 3 years?
  - A. Those with 3 episodes of wheezing per year and allergic rhinitis.
  - B. Those with 3 episodes of wheezing per year, aspirin allergy, and an episode of wheezing with a cold.
  - C. Those with 3 episodes of wheezing per year, blood eosinophilia, and aspirin allergy.
  - D. Those with 3 episodes of wheezing per year and exercise-induced wheezing.
  - E. Those with 3 episodes of wheezing per year, wheezing unrelated to colds, and allergic rhinitis.
2. A 14-year-old girl develops acute onset of shortness of breath with exercise. The shortness of breath resolves fairly quickly after cessation of exercise. Her discomfort is associated with breathing in vs breathing out. She is an accomplished athlete with a thin body habitus. She does not have a previous history of asthma or a family history of asthma. Which of the following is the MOST likely diagnosis for this young woman's condition?
  - A. Asthma.
  - B. Foreign-body aspiration.
  - C. Gastroesophageal reflux.
  - D. Oropharyngeal dysphagia with aspiration.
  - E. Vocal cord dysfunction.
3. A 10-year-old boy on the junior high school track team develops difficulty breathing associated with wheezing when running. Which of the following medications is the first-line therapy for this child?
  - A. Long-acting  $\beta_2$ -agonist before exercise.
  - B. Short-acting  $\beta_2$ -agonist before exercise.
  - C. Inhaled corticosteroid before exercise.
  - D. Leukotriene inhibitor before exercise.
  - E. Mast cell-stabilizing medication before exercise.
4. A 5-year-old girl is given a new diagnosis of asthma. After a brief discussion with her parents, the physician prescribes several medications. Which of the following medications is MOST likely to not be filled by her parents?
  - A. Long-acting  $\beta_2$ -agonist.
  - B. Short-acting  $\beta_2$ -agonist.
  - C. Inhaled corticosteroid.
  - D. Leukotriene inhibitor.
  - E. Mast cell-stabilizing medication.
5. A 4-year-old boy is newly diagnosed as having asthma. His parents are concerned about adverse effects of steroid medications. Which of the following is recommended to reduce adverse effects of steroid medications?
  - A. Distilled water in nebulizer.
  - B. Mouth rinse before inhalation.
  - C. Mycostatin mouth wash after inhalation.
  - D. Oral vs inhaled medication.
  - E. Spacer with metered-dose inhaler.

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