How Do You Diagnose Asthma in the Child?

CHAPTER 6

Joseph D. Spahn, Lora Stewart, and Bradley Chipps

- A group of young children with more than three episodes of wheeze can be identified as having high risk for continued symptoms and subsequent asthma (Table 6-1).
- Not all wheezing in children is the result of asthma. Appropriate diagnostic studies should be performed to rule out other causes of wheezing (Table 6-2).
- Pulmonary function studies in childhood asthma such as the FEV_1 are often normal.
- In older children with nonclassical presentation, bronchial challenge studies (i.e., methacholine or exercise testing) may be helpful.
- In young children, a diagnostic and therapeutic trial of controller therapy may be necessary to clarify the diagnosis.

DIAGNOSIS OF ASTHMA IN PRESCHOOL CHILDREN

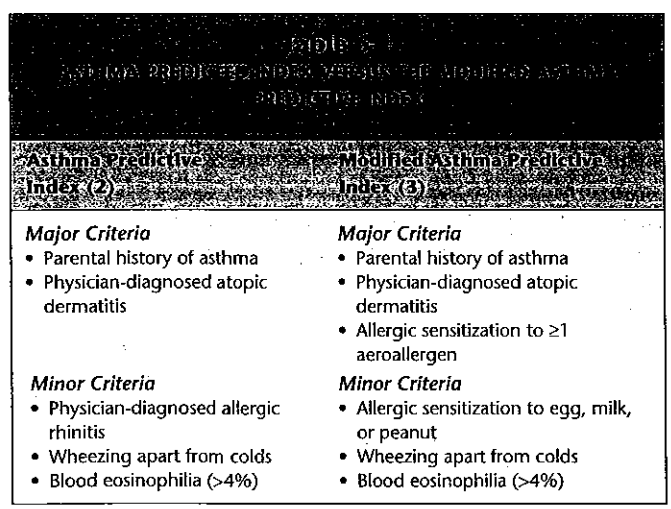
The diagnosis of asthma in preschool children is a challenge for many reasons. First and foremost, many preschool children with wheezing will not persist to be diagnosed with asthma. Large birth cohorts have shown that approximately 50% of preschool children with recurrent wheezing episodes will have only transient wheezing of childhood.[1] There is no single diagnostic test for asthma at any age group. Evaluations used in older patients to support an asthma diagnosis such as spirometry, exhaled nitric oxide, and sputum samples are not feasible in the preschool population. When considering a diagnosis of asthma in a younger child, many aspects of the current history, past history, and physical exam aid in distinguishing between transient wheezing and persistent asthma.

Important Aspects of the History of Present Illness

Recurrent or persistent respiratory symptoms often prompt consideration of a diagnosis of asthma. The most frequent presenting symptom is recurrent wheeze. Although many parents confuse wheeze with upper airway congestion or noise, previous physician-documented wheezing is helpful in confirming the presence of true wheeze. Often wheezing has been associated only with previous viral respiratory tract infections; however, it is important to clarify if any wheezing has been appreciated independent of obvious infection. Additional triggers of wheeze or respiratory symptoms may include exercise or activity, exposure to a furred or feathered animal, and environmental tobacco smoke. Cough is another important symptom that is often reported by caregivers. Persistent cough can be a sign of active disease. Unfortunately, cough is rather nonspecific, as most children will cough during childhood, especially with viral respiratory tract illnesses. A characteristic asthma cough is often described as dry and will often respond to bronchodilator therapy. Additionally, persistent cough apart from viral illness, especially nocturnal cough, is consistent with a diagnosis of asthma and a frequent nocturnal cough may be associated with more severe disease. Cough associated with activity such as exercise, laughing, or tickling is often related to asthma. Furthermore, a history of tachypnea, respiratory distress, or hypoxia is very helpful in assessing the severity of an episode and may help distinguish a simple upper respiratory infection from an episode of bronchospasm.

Important Aspects of Past Medical History

Birth history, specifically prematurity and a history of oxygen requirement and/or mechanical ventilation, is important to clarify in patients undergoing evaluation for recurrent respiratory symptoms. Patients born prematurely often develop chronic lung disease or bronchopulmonary dysplasia (BPD) and many also have airway hyperresponsiveness characteristic of asthma. Some studies have shown a lack of persistent inflammation in former premature infants with current asthma, and the condition may be different in this population compared with former term infants with current asthma. Nonetheless, former premature infant status is associated with increased risk of asthma, although prematurity is not associated with an increased risk of allergy. Additional risk factors in this population include very low birth weight, prolonged mechanical ventilation, and prolonged oxygen requirement.



Asthma Predictive Index (2)	Modified Asthma Predictive Index (3)
Major Criteria	*Major Criteria*
• Parental history of asthma	• Parental history of asthma
• Physician-diagnosed atopic dermatitis	• Physician-diagnosed atopic dermatitis
	• Allergic sensitization to ≥1 aeroallergen
Minor Criteria	*Minor Criteria*
• Physician-diagnosed allergic rhinitis	• Allergic sensitization to egg, milk, or peanut
• Wheezing apart from colds	• Wheezing apart from colds
• Blood eosinophilia (>4%)	• Blood eosinophilia (>4%)

Table 6-2
DIFFERENTIAL DIAGNOSIS OF RECURRENT WHEEZING

I. Upper Airway Conditions
  A. Allergic rhinitis
  B. Sinusitis
  C. Adenoidal hypertrophy
II. Large Airway Conditions
  A. Laryngotracheomalacia
  B. Vascular rings, laryngeal webs
  C. Tracheoesophageal fistula
  D. Foreign body aspiration
  E. Vocal cord dysfunction
  F. Vocal cord paresis/paralysis
  G. External mass compressing airway (e.g., tumor, or enlarged lymph nodes, congenital heart disease)
III. Small Airway Conditions
  A. Viral bronchiolitis (e.g., respiratory syncytial virus)
  B. Bronchopulmonary dysplasia
  C. Gastroesophageal reflux
  D. Bronchiolitis obliterans
  E. Diseases associated with bronchiectasis
    1. Cystic fibrosis
    2. B-cell immune deficiency
    3. Alpha$_1$-antitrypsin deficiency
    4. Primary ciliary dyskinesia
  F. Medications associated with chronic cough (e.g., angiotensin converting enzyme [ACE] inhibitors and beta-adrenergic antagonists)

It is important to clarify the details regarding the child's respiratory status during viral upper respiratory infections (URI) and when well. Children who have a history of cough or wheeze between episodes of URI are more likely to have persistent wheezing in the future compared to children with symptoms associated only with viral URIs. Additionally, children with frequent episodes of recurrent wheeze or cough (more than three per year) are more likely to have persistent disease.

The number of unscheduled visits to the primary physician, emergency or urgent care center visits, and hospitalizations can help determine the severity of the symptoms. Finally, a good response to previous therapies including bronchodilators and inhaled and systemic steroids is helpful in assessing the etiology of respiratory symptoms because a simple URI without associated bronchospasm will not be improved with the use of bronchodilator therapy or systemic steroids.

Infants and young children with the combination of atopic dermatitis and recurrent respiratory symptoms are at an increased risk for developing asthma. In the Tucson birth cohort, the presence of eczema was a major risk factor in predicting the likelihood of persistent disease.[2] Based on this cohort, an Asthma Predictive Index (API) was developed, as listed in Table 6-1. Major risk factors (only one is required) include parental asthma and physician-diagnosed atopic dermatitis. Minor risk factors (two are required) include physician-diagnosed allergic rhinitis, wheezing unrelated to colds, and blood eosinophilia (greater than or equal to 4%). The API has recently been modified based on a large early intervention study called the Prevention of Early Asthma in Kids (PEAK) study.[3] In this study, 2- to 3-year-old children with recurrent wheeze at risk for the development of persistent asthma were enrolled to receive 2 years of therapy with placebo or an inhaled glucocorticoid. Entry criteria included presence of one of three major criteria (parental history of asthma, physician-diagnosed atopic dermatitis, or allergic sensitization to 1 aeroallergen) or two minor criteria (allergic sensitization to milk, egg, or peanut; wheezing unrelated to colds; or blood eosinophils equal to 4%). As both eczema and asthma are atopic diseases, many children initially present with eczema with or without food allergies and then progress to develop asthma and finally allergic rhinitis or the so-called "atopic march."

Studies have shown that previous severe infection with respiratory syncytial virus (RSV), including hospitalization and/or oxygen requirement, is an independent risk factor for the development of asthma. It is still unclear whether the infection itself results in damage of the airway, which then results in the development of asthma, or if children predisposed to developing asthma are more vulnerable to experience a severe course when faced with infection by RSV. In either case, a history of a significant RSV infection may support a prediction of persistent disease.[4]

Important Aspects of the Family History

The evaluation of a child with recurrent respiratory symptoms should include a thorough review of the family medical history. Parental physician-diagnosed asthma is a major risk factor for persistent wheezing in a preschool-aged child with both infrequent and frequent episodes of wheezing. Reviewing the family history for the presence of other atopic disease such as allergic rhinitis, food allergy, and eczema will help establish a potential atopic genetic background for the patient.

Important Aspects of the Environmental History

An environmental history should be obtained to determine the presence of potential perennial allergens in the home; specifically, types of family pets both furred and feathered, whether the pets are indoor or outdoor, and if they sleep in the child's bedroom. In dust mite–endemic regions, the use of mattress and pillow covers; the frequency and manner of cleaning bedding; and the presence of carpeting, curtains, upholstered furniture, and stuffed animals should be included in an environmental history. Additional questions should address the presence of other potential irritants such as fireplaces or wood-burning stoves and the type of heat and air-cooling systems. Finally, the history should include environmental tobacco smoke exposure. Previous studies have shown that children who are sensitized to the allergens of house-dust mite and to the mold *Alternaria* are more likely to have asthma as documented by bronchial hyperresponsiveness.

Important Aspects of the Physical Exam

There are several portions of the physical exam that may support atopic disease in a young child with recurrent wheeze. Examination of the nose will often reveal edema and rhinorrhea, but unfortunately it is nearly impossible to differentiate allergic rhinitis from viral upper respiratory illnesses. When performing a lung exam on a well-appearing child, the respiratory rate, inspiratory-to-expiratory phase ratio, oxygen saturation, and auscultation will likely be normal. As such, a normal lung exam during a well time does not rule in or rule out the diagnosis of asthma. During an acute episode, the lung exam will be most helpful. Documentation of wheezing,

tachypnea, retractions, and/or hypoxia is important in characterizing the symptoms and severity of an episode. Skin examination is important in determining whether the child has any concomitant atopic dermatitis, specifically looking for erythema, excoriations, thickening, or lichenification. In the preschool age group, the distribution of eczema may include the face and extensor regions seen in infancy or be transitioning to the flexor regions as seen with the older age groups.

Testing Options in the Younger Child

LUNG FUNCTION TESTING

In the older child, lung function tests such as spirometry and lung volume measurements (body plethysmography) are often helpful in confirming or excluding a diagnosis of asthma. In this situation, improvement in airflow obstruction by 12% is supportive of the diagnosis. Unfortunately, these tests require both cooperation and coordination to complete. In the preschool-aged child, lung function testing is possible, but its regular application is limited by the requirement for sedation, costly equipment, and specialized personnel.

Infant Pulmonary Function Tests

In infants, several techniques are available to quantitate lower airway function. At present, these techniques are used in research and normative values are not available from large cohorts. The available techniques include measurement of lung volumes (body plethysmography or gas dilution), partial expiratory flow volume curves (thoraco-abdominal compression), or rapid interruption of expiratory flow to measure airway resistance (Rint). These methods are labor intensive and usually require sedation of the infant. These tests may be used in clinical situations such as (1) unexplained tachypnea, cough, hypoxemia, or respiratory distress where a definitive diagnosis is not clear; (2) in children with lower airway symptoms who are not responding to standard therapy; (3) to determine the severity of lower airway obstruction and provide basis for follow-up after intervention; and (4) in research studies to better define the course of diseases and response to therapy. It is hoped that further advances will allow for wider application of this technology as equipment becomes more affordable and easier to use, and better normative standards become available.

Impulse Oscillometry

Impulse oscillometry (IOS) is a newer technology that uses small-amplitude pressure oscillations to determine the resistance of the airway. It is largely independent of effort and does not require coordination, but does require cooperation of the child, which is a limiting factor for routine use. To perform IOS, the child holds a mouthpiece in place over a 30-second period of time while breathing normally (tidal breathing). Sound impulses of various frequencies from 5 to 35 Hz are applied to the airway through the mouthpiece with total respiratory system resistance (Rrs) and reactance (Xrs) determined at the various frequencies. IOS has been studied in young children with suspected asthma with conflicting results obtained. While some investigators have not found IOS to be useful in differentiating recurrent wheezers from healthy preschool children, others have found significant differences in both baseline Rrs and change in Rrs following inhalation of a beta-agonist in asthmatic compared with nonasthmatic children. Last, young children at risk for asthma have a significant change in Rrs following bronchodilator compared with age-matched control children. Thus, IOS may become a useful measure in young children with suspected asthma, but at present it remains largely a research tool.

In older children and adults who are able to complete spirometry, a bronchial challenge (methacholine, histamine, or exercise) demonstrating airway hyperresponsiveness is strongly supportive of a diagnosis of asthma. Younger children are unable to voluntarily complete spirometry; therefore, the bronchial challenge has been modified by incorporating auscultation and pulse oximetry monitoring. Currently, the presence of wheeze, significant tachypnea, and/or a 5% or more decrease in oxygen saturation from baseline constitutes a positive challenge. Unfortunately the test is not standardized and there has been dispute as to the best parameter to confirm positivity. These issues aside, there is evidence that more severe degrees of airway hyperresponsiveness are correlated with increased likelihood of disease persistence or development.

OTHER TESTS

Radiographic studies such as chest x-rays and chest computed tomography (CT) scans of young children with a history of recurrent wheezing or cough are not routinely obtained during well periods. The usefulness of radiographic studies during acute wheezing episodes has been debated and is usually reserved for patients with significant tachypnea, localized findings on auscultation, associated fever, or significant hypoxemia. Additionally, chest radiographs can be useful when concern exists about a foreign body or the presence of an anatomical abnormality.

Demonstration of specific immunoglobulin (Ig) E either by percutaneous skin prick testing or radioallergosorbent test (RAST) of serum can confirm atopy in a child. Because it takes several seasons to develop sensitization to seasonal aeroallergens, skin testing in the preschool-aged child is confined to perennial allergens (dust mite, mold, and pet dander) or food allergens if this is a concern for an individual patient. Unfortunately, negative testing does not rule out atopy but merely confirms that there is currently no sensitization to the allergens tested. A negative test at a young age does not predict whether the child might develop sensitization in the future.

Additional laboratory results such as an elevated eosinophil count or elevated serum IgE level may suggest atopy, but are much less specific. An elevated eosinophil count is considered a minor criterion for predicting persistence as defined by the API and modified API.[2,3]

In patients in whom there is concern for recurrent infection as the etiology of recurrent wheeze or cough, an immune system evaluation may be warranted including quantitative immunoglobulin levels (IgG, IgM, and IgA) and assays for functional antibody. Typically, patients with underlying immunodeficiency have additional signs and symptoms apart from recurrent wheeze or cough such as recurrent fever, failure to thrive, and documented bacterial infections. Cystic fibrosis (CF) must also be considered in any young child presenting with a history of recurrent or persistent respiratory symptoms. Classically, CF presents with additional symptoms of failure to thrive or evidence of pancreatic insufficiency, but

milder variants of CF exist and can be ruled out by a normal sweat test (<30 mEq/L Cl^- in children <2 years old) or demonstration of the absence of a CF DNA mutation.

Some patients will present with recurrent episodes of choking or aspiration or a history of gastroesophageal reflux symptoms in addition to recurrent wheeze or cough. These patients warrant evaluation for swallowing dysfunction, aspiration, or gastroesophageal reflux disease (GERD) by barium swallow and/or pH probe study. These problems are not infrequently found in combination with underlying bronchial hyperresponsiveness and treatment often results in improvement of both problems.

Finally, in patients with a history of inspiratory stridor or wheeze, or patients who have failed to respond to bronchodilator therapy or a short course of systemic steroids, tracheomalacia must be considered. Although diagnosis can often be made clinically, the diagnosis and severity assessment can also be made by bronchoscopy.[5]

Summary

Although predicting the likelihood of persistent asthma in a preschool-aged child with recurrent or persistent respiratory symptoms is difficult, the presence of several risk factors including personal history of eczema or allergic rhinitis, parental history of asthma, positive allergy skin tests, and persistence of symptoms without viral illnesses will aid in the diagnosis. Additionally, one must consider other potential causes of recurrent respiratory symptoms, including GERD, tracheomalacia, or cystic fibrosis. Finally, a number of tests are available to support a diagnosis of asthma or the risk of future asthma such as skin prick testing, blood work documenting atopy (eosinophilia or elevated IgE level), or even documentation of bronchial hyperresponsiveness.

DIFFERENTIAL DIAGNOSIS OF RECURRENT WHEEZE IN PRESCHOOL CHILDREN

When evaluating a preschool-aged child with recurrent wheezing or other respiratory symptoms, the differential diagnosis is quite extensive, but it can be narrowed based on a thorough history and physical examination (see Table 6-2). Additionally, the practitioner should focus on common conditions such as asthma, GERD, and upper airway diseases such as rhinitis and sinusitis unless the evaluation supports pursuing rare etiologies.

GERD is a common diagnosis in young children. Often this age group does not complain of the classic symptoms of heartburn or abdominal pain, but rather presents with excess burping or emesis, coughing after meals, or nocturnal cough or wheeze. Diagnosis can be suspected clinically and confirmed with positive response to empiric therapy with an acid suppression regimen. Alternatively, a pH probe to document increased or prolonged events of acid in the esophagus or radiographic studies may be used before treatment is started. Because GERD and asthma symptoms may coexist, a diagnosis of one or the other is not mutually exclusive, but previous studies have shown that treatment of GERD may result in improved asthma symptoms and decreased need for asthma medication.

Chronic sinusitis or rhinitis with associated postnasal drip may contribute to persistent cough in the preschool-aged patient. Typically, patients have evidence of persistent nasal congestion or drainage in association with the cough. The cough is more likely to be wet and/or productive and worse at night or early morning. This type of cough will not improve with bronchodilator therapy or inhaled corticosteroid therapy, but does often improve with treatment of the underlying condition. Treatment can be started empirically, but a sinus CT may also be useful if considering a prolonged antibiotic course.

Tracheomalacia, or abnormal tracheal cartilage, is a common anatomic defect seen in young children. Patients often present with recurrent episodes of stridor, wheeze, or barky cough, which is worsened by crying and concurrent respiratory infection. Respiratory symptoms often subside while sleeping, in contrast to asthma where symptoms often worsen at night. In many patients the symptoms are present between episodes of infection, but mild cases may only be symptomatic with infection or vigorous crying. Additionally, treatment with a bronchodilator results in no change or even worsens symptoms because it results in diminished tone in the presence of malacia. Glucocorticoids, both systemic and inhaled, are also ineffective. For most patients the symptoms will resolve by age 2, but more persistent disease can occur. Evaluation for potential etiologies, including tracheoesophageal fistula, vascular ring, or underlying connective tissue disorder, should be pursued for severe or persistent presentations. Bronchoscopy is the study of choice in the diagnosis and assessment of tracheomalacia.

Mechanical airway compression due to congenital cardiac anomalies should be considered in a patient with recurrent respiratory symptoms that have failed to improve with bronchodilator or corticosteroid therapy. Anatomic compression is obviously a less common etiology for recurrent wheeze compared to asthma, but is often unrecognized in this age group. Compression can occur due to vascular rings or slings (right-sided or double aortic arch, anomalous innominate artery, or pulmonary artery sling) or enlargement of cardiac and/or pulmonary vasculature (dilated pulmonary arteries, left atrial enlargement, or massive cardiomegaly). A classic presentation includes recurrent respiratory difficulties with wheezing and stridor. Many patients have associated dysphagia or apnea. The symptoms are usually aggravated by crying and concurrent respiratory viral infections. The severity of symptoms is dependent on the location and the degree of the anomaly. When this diagnosis is suspected, a chest x-ray should be obtained with close attention to the side of the aortic arch, size and shape of the cardiac silhouette, and for the presence of tracheal deviation or constriction. Esophagrams are often used to evaluate for vascular rings and slings, but are nonspecific and may be normal despite the presence of an anomaly if that anomaly does not compress the esophagus. Of note, bronchoscopy is not diagnostic; magnetic resonance imaging (MRI) of the chest or angiography is required to confirm the diagnosis. Finally, congestive heart failure in young children rarely presents with wheezing, but may present with a history of increased work of breathing.

The rare H-type tracheoesophageal fistula (TEF) may need to be considered in a patient with recurrent respiratory symptoms, usually recurrent pneumonia or persistent infiltrate on chest radiograph. These patients will not respond to conventional therapies including bronchodilators and corticosteroids. The vast majority of patients with TEF have additional birth

anomalies. This type of TEF is often difficult to demonstrate by conventional radiographic studies and may require bronchoscopy, possibly in combination with esophageal motility studies, as GERD is a common comorbidity.

In a preschool-aged patient with acute onset of wheeze and/or cough, foreign body (FB) aspiration must be considered. On physical exam, the wheezing will often be unilateral or localized. A forced expiratory chest radiograph may demonstrate air trapping behind the foreign body. The diagnosis is confirmed by bronchoscopy and removal of the FB. Typically, patients present with acute respiratory symptoms, but chronic symptoms or a history of infiltrate or pneumonia that fails to clear can occur as well.

Patients with CF classically present with a history of recurrent respiratory symptoms in association with systemic symptoms of failure to thrive, diarrhea, and recurrent sinus and ear infections. Additionally, there are many more mild variants to classic CF that may not have associated systemic symptoms. Therefore, in a patient with recurrent pneumonia or who has failed to respond to conventional therapies, one should consider CF in the differential diagnosis.

Immunodeficiency presenting with only recurrent wheeze and/or cough without superimposed infections, diarrhea, rash, or failure to thrive is quite rare. Immunodeficiency should not be considered in the initial differential diagnosis of a young child with only recurrent wheeze and/or cough.

Summary

In summary, when evaluating a preschool-aged child with recurrent wheezing or other respiratory symptoms, first consider the most common etiologies unless there are additional findings in the history or physical that point to a more rare explanation for the symptoms.

DIAGNOSIS OF ASTHMA IN SCHOOL-AGED CHILDREN

Important Aspects of the History of Present Illness

Similar to those in younger children, recurrent or persistent respiratory symptoms often prompt the consideration of asthma in school-aged children. The most frequent presenting symptoms are recurrent cough and wheeze. As many parents confuse wheeze with upper airway congestion, previous physician-documented wheezing is most helpful in confirming the presence of true wheeze. Wheezing may occur only with viral respiratory tract infections, but the parents may have noted wheezing or other respiratory symptoms with exercise, animal exposure, cold air, or environmental tobacco smoke exposure. Cough is another important symptom as persistent cough can be a sign of active disease. Although very sensitive, cough is nonspecific, as most children will cough during childhood. Important clues to cough being associated with asthma include a nocturnal predominance, exaggerated cough with exercise or cold air, and cough that improves in frequency and/or severity following controller therapy. Chest tightness is another symptom reported by children. The location of chest tightness is also important to delineate, as it can be helpful in differentiating tightness associated with vocal cord dysfunction, which is localized to the neck and throat, from chest tightness associated with lower airway flow limitation. Last, the presence of eczema or nasal symptoms consistent with allergic rhinitis strengthens the likelihood of asthma in a child with recurrent cough or wheeze, as 80% to 90% of all school-aged children with asthma have an allergic diathesis.

Important Aspects of Past Medical History

As mentioned previously, history of preterm birth and a history of oxygen requirement and/or mechanical ventilation are important to clarify in patients undergoing evaluation for possible asthma. Inquiry into the frequency and severity of past wheezing episodes provides information with respect to level of severity and control. Has the child ever required an urgent care or emergency room visit or hospitalization for respiratory difficulties? Equally important is determining whether the child's respiratory symptoms worsen with viral respiratory tract infections and whether wheezing occurs apart from colds. Other important questions include the following: Does the child have a seasonal component to his or her symptoms? Has the child ever been treated with bronchodilators or controller therapy for previous episodes? If so, has the treatment resulted in improvement? Last, has the child's lung function ever been tested? If so, was the lung function diminished and did it improve with bronchodilator?

Important Aspects of the Family History

The evaluation of a child with recurrent respiratory symptoms should include a thorough review of the family medical history. The presence of nasal allergies, food allergy, eczema, or asthma in siblings, grandparents, or parents is often noted in children with asthma.

Important Aspects of the Physical Exam

There are several components of the physical exam that can aid in the diagnosis of asthma. When examining the eyes and nose, look for the presence of conjunctival injection, allergic shiners, a nasal crease, and the presence of boggy, pale inferior turbinate edema with clear nasal discharge, which are the classic features of allergic rhinoconjunctivitis. As roughly 70% of children with asthma have allergic rhinitis, the presence of rhinitis in a child with lower respiratory symptoms supports asthma as the diagnosis. The presence of nasal polyps should always prompt evaluation for CF, as polyps are far more frequently encountered in children with CF compared with allergic rhinitis and asthma. Nasal polyps in childhood asthma are relatively rare. They are much more commonly encountered in adults with aspirin-sensitive asthma.

When performing a lung exam on a well-appearing child, respiratory rate, inspiratory-to-expiratory phase ratio, chest auscultation, and oxygen saturation will often be normal. As such, a normal lung exam does not exclude the diagnosis of asthma. In fact, many children with chronic severe, yet stable asthma will have clear lungs on auscultation despite having significant airflow limitation. In contrast to the lung exam in stable asthma, it is helpful during acute attacks where diminished air exchange, wheezing, tachypnea, retractions, and/or hypoxia are often present and can be used to characterize the severity of the episode. In some children, wheezing may

be absent despite significant respiratory distress. Only after several bronchodilator treatments does air exchange improve enough for wheezing to be appreciated.

Examination of the skin should always be performed, as the presence of atopic dermatitis in a child with recurrent wheezing strongly supports the diagnosis of asthma. One should specifically look for erythema, excoriations, and thickening or lichenification of the skin. The distribution of skin involvement is largely age dependent. In the preschool age group, the distribution of eczema often includes the face and extensor regions, while the flexor regions and neck are often involved in school-aged children and adolescents.

Testing Options in the Older Child

LUNG FUNCTION TESTING

Peak Expiratory Flow

The peak expiratory flow (PEF) is the maximum flow obtained within the first 200 milliseconds of a forced expiratory maneuver after inhalation to total lung capacity (TLC). PEF meters are portable, inexpensive, and easily used. Peak flow monitoring in patients with known asthma is useful in monitoring disease activity and response to pharmacologic intervention. Whether it is useful as a diagnostic tool is less clear. A recent study comparing PEF variability to methacholine responsiveness in subjects with suspected asthma found PEF variability a poor substitute for methacholine challenge.[6]

Spirometry

Spirometry is among the most important tests of lung function in asthma. With adequate coaching, children as young as 5 years can perform the maneuver. When performing spirometry, inspection of the volume-time curve allows an assessment of the adequacy of the child's expiratory effort (Fig. 6-1). An acceptable test requires an older child to exhale for at least 6 seconds. Patients with airflow limitation will have a characteristic concave or "scooped out" expiratory flow-volume loop as seen in Figure 6-1. The inspiratory flow volume loop should have the appearance of a semicircle. A blunted or scalloped appearance, as illustrated in Figure 6-2, is suggestive of inappropriate closure of the vocal cords as is seen in vocal cord dysfunction (VCD), a frequent masquerader of asthma.

The FEV_1 (forced expiratory volume in 1 second) is the gold standard measure for diseases characterized by airflow limitation such as asthma, CF, and chronic lung disease of prematurity. According to NHLBI asthma guidelines,[7] patients

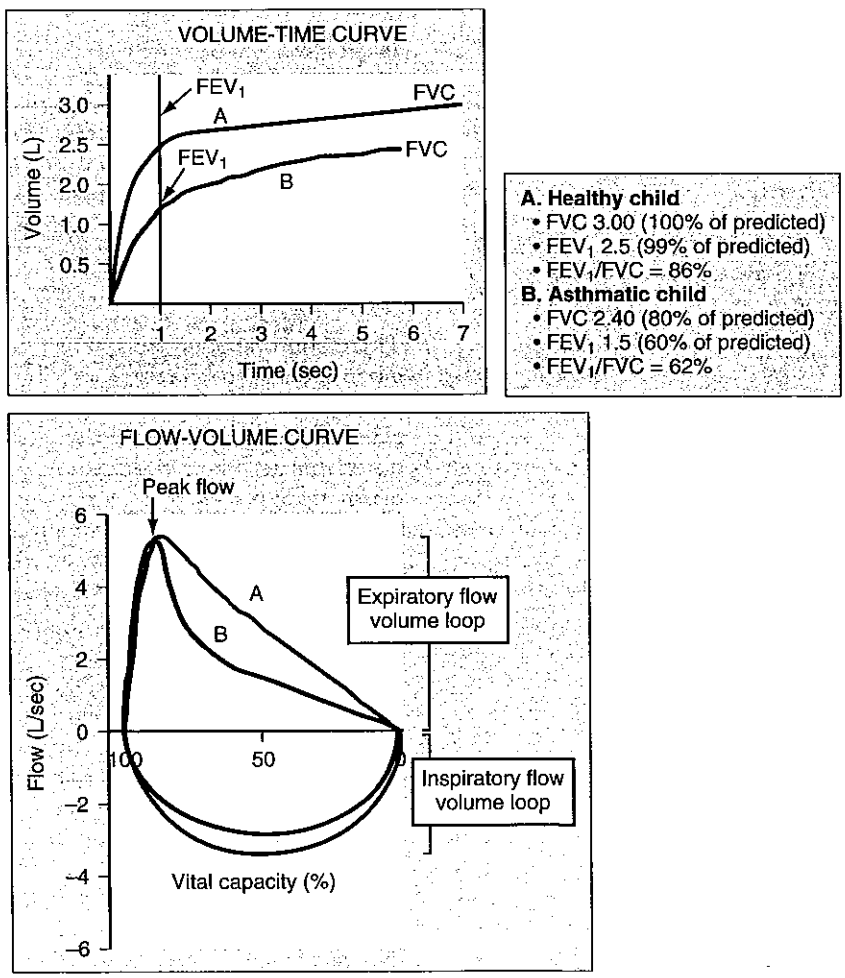


Figure 6-1 Volume-time and flow-volumes curves from a healthy control and an asthmatic child demonstrating significant decrease in FEV_1 in the asthmatic child compared with the nonasthmatic child. Both children have adequate expiratory times. The flow-volume curve in the asthmatic child demonstrates airflow obstruction with the characteristic concave appearing expiratory flow volume loop. Both children have normal inspiratory flow volume loops. Of note, despite the diminished FEV_1 and FEV_1/FVC ratio, the asthmatic child had a normal PEF.

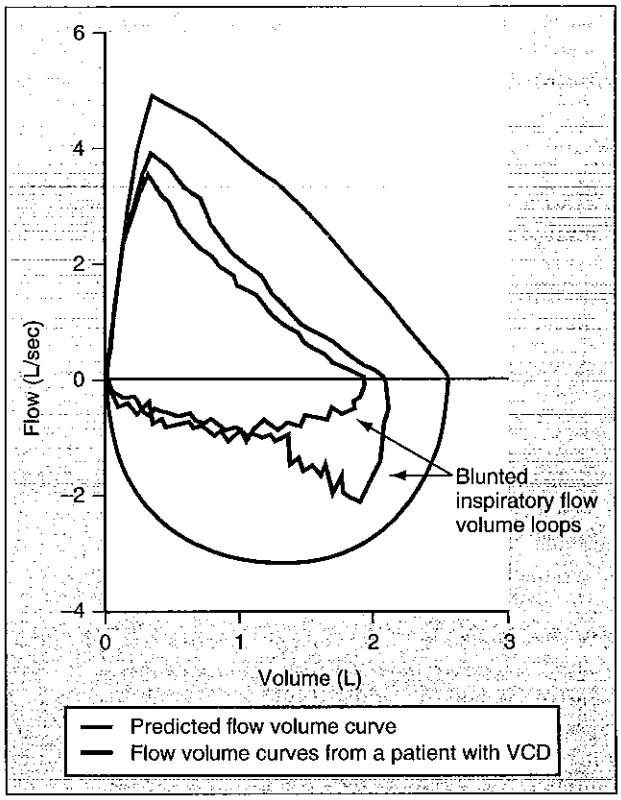


Figure 6-2 Flow volume curves from a patient with vocal cord dysfunction. The FEV_1 and FVC are proportionally impaired at 75% of predicted while the FEV_1/FVC ratio is normal, indicating the absence of flow limitation. Evaluation of the inspiratory flow-volume loop reveals significant blunting caused by inappropriate closure of the vocal cords.

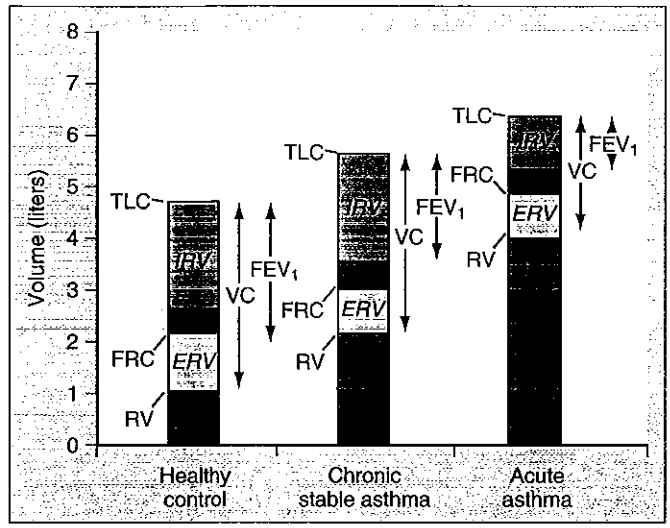


Figure 6-3 Lung volume measurements in a nonasthmatic individual, a chronic yet stable asthmatic individual, and in an asthmatic patient during an acute asthma attack. Note that the RV is most profoundly affected during an acute asthma attack. Also note that the RV increases more disproportionately than the TLC. As a result, the patient's inspiratory and expiratory reserve volumes (IRV, ERV) shrink substantially.

with mild asthma have FEV_1 values of more than 80%, those with moderate persistent asthma have values 60% to 80%, and those with severe persistent asthma have FEV_1 values of less than 60% of predicted. The FEV_1 primarily measures flow through the mid- to large-sized airways. Of importance, children with asthma often have normal FEV_1 values when well. As a result, a normal value does not rule out asthma.

The FEV_1/FVC ratio is the amount of air exhaled in the first second divided by all of the air exhaled during a maximal exhalation. The FEV_1/FVC ratio is highest in young children (>90%) and decreases with increasing age. A normal FEV_1/FVC ratio in children is 86%, with values below 80% indicative of airflow limitation. Studies evaluating the association between lung function and asthma severity based on the NHLBI asthma guidelines have found the FEV_1/FVC ratio to be a more sensitive measure of severity versus the FEV_1.

The forced expiratory flow between 25% and 75% of vital capacity (FEF_{25-75}) measures airflow in the mid-portion of the vital capacity. It is largely effort independent and it is thought to be a measure of peripheral airway obstruction. The FEF_{25-75} is among the first parameters to be abnormal in pediatric asthma, and it is often the most significantly impaired of all of the spirometric measures. It is the impairment in the FEF_{25-75} that gives the expiratory flow volume curve the characteristic scooped out or concave appearance (see Fig. 6-1). The FEF_{25-75} is another sensitive measure of airflow limitation in children as demonstrated by Paull and co-workers,[8] who analyzed over 24,000 lung function measures in 2728 asthmatic children evaluated at a tertiary referral center. The mean FEV_1 of the cohort studied was 92.7% of predicted, with 77% of the values within the normal range (>80% of predicted). In contrast, the mean FEF_{25-75} was 78% with only 27.7% of the values greater than 80% of predicted, while 30.4% were between 60% and 80%, and 40.9% were less than 60% of predicted.

Assessment of Lung Volumes

There are two ways to assess lung volume: helium dilution and body box plethysmography. Of the two techniques, body plethysmography is the preferred method as helium dilution can underestimate air trapping in patients with severe airflow obstruction. The first and most consistently elevated lung volume measure in asthma is the residual volume (RV) (Fig. 6-3). With increasing asthma severity, the RV increases followed by an increase in the functional residual capacity (FRC) and the total lung capacity (TLC). The RV is also the last measure to normalize following an asthma exacerbation.

MEASURES OF AIRWAY HYPERRESPONSIVENESS

Airway Hyperresponsiveness

Airway hyperresponsiveness (AHR) can be measured by naturally occurring stimuli (cold air challenge or exercise) or pharmacologic stimuli (methacholine, histamine, mannitol, and adenosine monophosphate [AMP]). These measurements may be used to establish the diagnosis of asthma and monitor disease progression and response to therapy. The two most commonly employed tests in children are exercise and methacholine challenge. The methacholine challenge has both high sensitivity and specificity making it the gold standard measure to diagnose asthma. A positive challenge is noted when the FEV_1 falls 20% or more at no more than 8 mg/mL of methacholine (Fig. 6-4). When a methacholine challenge is negative (<20% drop in FEV_1 at 8 mg/mL), the diagnosis of asthma is in doubt.

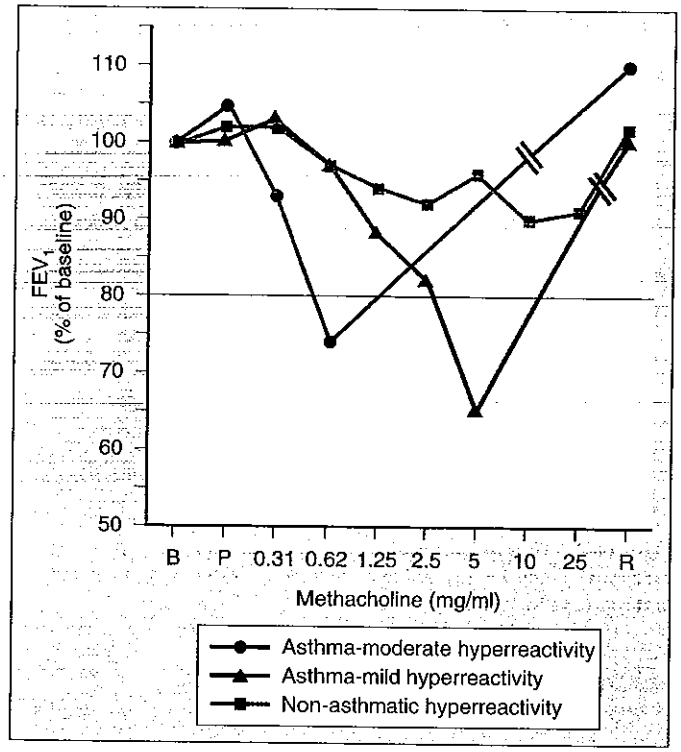


Figure 6-4 Methacholine dose response curves from three children. Two of the children had methacholine PC_{20} FEV_1 values of less than 8 mg/mL and were known asthmatic patients. The third child had recurrent cough, normal spirometry, and no beta-agonist reversibility. A methacholine challenge revealed the child to have normal airway reactivity with a PC_{20} value of greater than 25 mg/mL making the diagnosis of asthma unlikely.

Methacholine challenges are not widely performed in clinical practice because of their high cost, need for trained personnel, and limited availability.

Exercise-induced asthma is a common trigger for asthma with a prevalence of exercise-induced bronchospasm (EIB) of up to 80% in young asthmatic patients. Standard exercise protocols require patients to exercise at 85% of maximum predicted heart rate for 6 to 10 minutes while continuously monitoring heart rate and Sao_2. Spirometry is done at baseline and 1, 5, and 10 minutes after exercise. A positive test is defined as a 15% drop in FEV_1 or 20% drop in peak flow from baseline.

Beta-Agonist Reversibility

Beta-agonist reversibility allows for assessment of reversibility of airflow limitation and should be done even if the baseline FEV_1 is within the normal limits. Not only is beta-agonist responsiveness (12% improvement in FEV_1 or an increase of 200 mL) helpful in making the diagnosis of asthma, but the degree of beta-agonist reversibility also correlates with airway inflammation. Covar and colleagues[9] evaluated the clinical utility of two noninvasive measures of airway inflammation, exhaled nitric oxide (eNO) and sputum eosinophils, in children with mild to moderate asthma and found neither sputum eosinophilia nor eNO levels to correlate with baseline FEV_1 values, while both correlated with the change in FEV_1 following a bronchodilator.

OTHER TESTS

Radiographic studies such as chest x-rays are often performed in children with suspected asthma mainly to rule out other causes of cough or wheeze and have little diagnostic utility. The usefulness of radiographic studies during acute episodes has been debated and is usually reserved for patients with significant tachypnea or hypoxemia, localized findings on auscultation, or associated fever.

Demonstration of specific IgE either by percutaneous skin prick testing or RAST testing of serum is important in ascertaining atopy. Skin testing in the school-aged child should include a panel of seasonal aeroallergens including representative trees, grasses, and weeds in addition to outdoor molds. Perennial allergens such as dust mite, cockroach, molds, and pet dander should also be evaluated. Food allergens should be tested only if food allergy is suspected. Not only do the presence of positive skin tests indicate the presence of atopy, but they also identify triggers for both upper and lower airway symptoms.

Elevated circulating eosinophil counts or elevated serum IgE levels may suggest atopy, but are neither sensitive nor specific markers for asthma. In patients in whom there is concern for recurrent infection as the etiology of recurrent wheeze or cough, an immune system evaluation may be warranted including quantitative immunoglobulin levels (IgG, IgM, and IgA).

Gastroesophageal reflux (GER) is common in children with asthma. GER should be considered in children with difficult to control asthma and in children with significant nocturnal symptoms. These patients warrant evaluation for GER by barium swallow and/or pH probe study.

Finally, in patients with a history of inspiratory stridor or audible wheeze, or patients who have failed to respond to bronchodilator therapy, vocal cord dysfunction (VCD) must be considered. VCD is among the most common masqueraders of asthma in older children and adolescents.[10] Although diagnosis can often be made from the characteristic blunting of the inspiratory flow volume loop, the diagnosis and severity of paradoxical vocal cord closure is made by flexible laryngoscopy.

Summary

Making the diagnosis of asthma in a school-aged child is accomplished by obtaining pertinent information regarding type, frequency, and severity of symptoms in addition to determining the presence of risk factors, such as a parent with asthma or the coexistence of atopic dermatitis. Additionally, airflow limitation that improves following bronchodilator in a child with lower respiratory symptoms strongly supports the diagnosis of asthma. The presence of atopy and associated allergic conditions such as allergic rhinitis also lends support to the diagnosis of asthma. Last, in cases that remain difficult to determine, a methacholine challenge can be performed. A positive methacholine challenge in a child with lower respiratory symptoms is diagnostic of asthma, whereas a negative test does not support the diagnosis.

DIFFERENTIAL DIAGNOSIS OF RECURRENT WHEEZE OR COUGH IN SCHOOL-AGED CHILDREN

When evaluating a school-aged child with recurrent cough or wheezing, the differential diagnosis is not as extensive as it is for young children and it can be narrowed based on a thorough

history and physical examination. The most common conditions include asthma, gastroesophageal reflux, sinus disease, vocal cord dysfunction, and chronic cough, unless the evaluation supports pursuing rare etiologies.

Gastroesophageal Reflux Disease

Recent studies show a general prevalence of gastroesophageal reflux in school-aged children with asthma of between 47% and 75%, which is similar to adults with asthma, and about two to four times the prevalence in the general population. Although respiratory symptoms in asthmatic adults are often associated with reflux, asthmatic children often deny heartburn, regurgitation, and dysphagia. As such, GER must always be considered, even in the absence of symptoms, in children with asthma or suspected asthma, particularly in children who have difficult-to-control asthma. As the case for young children with asthma, 24-hour pH monitoring is considered the gold standard for documenting the presence of GER. Other tests, such as barium swallow and endoscopy, while providing important data, are neither sensitive nor specific for the diagnosis of GER.

Sinusitis

Radiographic evidence for sinus disease is often noted in children with asthma. Mounting data link the physiology of the upper and lower airways and support the hypothesis that the same pathology underlies both sinusitis and asthma. Studies demonstrate that inflammation of the nose and sinuses is associated with lower airway hyperresponsiveness, and that nasal allergen challenge results in airway hyperresponsiveness and eosinophilia of both the upper and lower airways.

Treatment of the upper airway, generally with nasal glucocorticoids, has been shown to ameliorate lower airway hyperreactivity in children with asthma. In addition, significant improvement in asthma control can occur when sinus disease is recognized and appropriately treated. A screening CT scan of the sinuses provides greater resolution and thus greater sensitivity than conventional sinus radiographs and should be used when evaluating for sinusitis.

Vocal Cord Dysfunction

VCD, defined as inappropriate or paradoxical adduction of the vocal cords during inspiration, is among the most common masqueraders of asthma in older children and adults. In addition, children can have both VCD and asthma. VCD must be suspected in all patients who have frequent or unremitting symptoms, as this condition can be misdiagnosed as refractory asthma leading to overtreatment.[10]

VCD is frequently triggered by many of the same triggers as asthma (e.g., irritants, exercise, postnasal drip, GERD, emotions) and as such is easily mistaken by patients and physicians as asthma. Questioning the patient for symptoms prominent in the throat and on inspiration may reveal this diagnosis, although many patients are unable to localize symptoms to the throat. Importantly, a history of nocturnal abatement of symptoms and lack of response to bronchodilators may guide the physician to this diagnosis. The finding of stridor or inspiratory wheeze that is loudest at the neck, but often radiating throughout the chest during an acute episode is also suggestive of the diagnosis.

Because all routine monitoring of expiratory function in asthma requires maximal inspiration before a maximal expiratory effort, both PEF and FEV_1 measures can be falsely decreased and misleading. The FVC may also be falsely diminished, and hence, the FEV_1/FVC ratio will often remain in the normal range and not show evidence of obstruction typical of asthma (Fig. 6-2). Inspiratory flow volume loops are indispensable for the interpretation of the forced expiratory maneuvers. Truncation or irregularity of the flow volume loop on inspiration, and a forced inspiratory fraction and forced expiratory fraction at 50% of vital capacity (FIF_{50}/FEF_{50}) of greater than 1 is highly suggestive of obstruction of the extrathoracic airway, but like the findings above, may only be present during a symptomatic episode. Although evaluation of the inspiratory flow volume loop is suggestive of VCD, the gold standard remains direct visualization of vocal cord motion by flexible rhinolaryngoscopy during a symptomatic episode.

Summary

The diagnosis of asthma in childhood is primarily based on frequency, quality, and severity of symptoms in addition to family history and other allergic comorbidities (see Table 6-1). Response to therapy can be especially helpful as a diagnostic tool in younger children where pulmonary function testing can be a challenge. The differential diagnosis of recurrent wheezing is especially large in infants and toddlers and testing to rule out other conditions should be performed in a thoughtful manner (see Table 6-2). Alternative diagnoses or comorbid conditions must be appropriately evaluated and treated. The key to the diagnosis of asthma in children includes a high index of suspicion, as 80% of asthma starts before the age of 5 years. The clinical course will reflect the variability of childhood asthma, with some patients having long periods of quiescent symptoms, but this should not prevent appropriate diagnoses and treatment when supported by the appropriate clinical presentation.

REFERENCES

1. Martinez FD, Wright AL, Taussig LM, Holberg CJ, Halonen M, Morgan WJ: Asthma and wheezing in the first six years of life. N Eng J Med 1995;332:133–138.
2. Castro-Rodriquez JA, Holberg CJ, Wright AL, Martinez FD: A clinical index to define risk of asthma in young children with recurrent wheezing. Am J Respir Crit Care Med 2000;162:1403–1406.
3. Guilbert TW, Morgan WJ, Zeiger RS, et al: Atopic characteristics of children with recurrent wheezing at high risk for the development of childhood asthma. J Clin Immunol 2004;114:1282–1287.
4. Sigurs N, Bjarnason R, Sigurbergsson F, Kjellman B: Respiratory syncytial virus bronchiolitis in infancy is an important risk factor for asthma and allergy at age 7. Am J Respir Crit Care Med 2000;161:1501–1507.

5. Saglani S, Nicholson AG, Scallon M, et al: Investigation of young children with severe recurrent wheeze: any clinical benefit? Eur Respir J 2006;27:29–35.
6. Goldstein MF, Veza BA, Dunsky EH, Dvorin DJ, Belecanech GA, Haralabatos IC: Comparisons of peak flow diurnal expiratory flow variation, postbronchodilator FEV1 responses and methacholine inhalation challenges in the evaluation of suspected asthma. Chest 2001;119:1001–1010.
7. National Institutes of Health, National Heart, Lung, and Blood Institute: National Asthma Education and Prevention Program. Executive summary of the NAEPP expert panel report. Guidelines for the diagnosis and management of asthma—update on selected topics 2002 (NIH Publication No. 02-5075). Rockville, Md, U.S. Department of Health and Human Services, June 2002.
8. Paull K, Covar R, Jain N, Gelfand EW, Spahn JD. Do the NHLBI lung function criteria apply to children? A cross-sectional evaluation of childhood asthma at National Jewish Medical Center 1999–2002. Pediatr Pulmonol 2005;39:311–317.
9. Covar RA, Szefler SJ, Martin R, et al: Relationships between exhaled nitric oxide and measures of disease activity among children with mild to moderate asthma. J Pediatr 2003;142:469–475.
10. Christopher KL, Wood RP, Eckert RC, et al: Vocal-cord dysfunction presenting as asthma. N Engl J Med 1983;308:1566–1570.